Impact factor 5.49

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control

Vol. 18 | Weekly issue 32 | 08 August 2013

Research articles

Surveillance and outbreak reports

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Impact of universal two-dose vaccination on varicella epidemiology in Navarre, Spain, 2006 to 2012

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Citation style for this article:
García Cenoz M, Castilla J, Chamorro J, Martínez-Baz I, Martínez-Artola V, Irisarri F, Arriazu M, Ezpeleta C, Barricarte A. Impact of universal two-dose vaccination on varicella epidemiology in Navarre, Spain, 2006 to 2012. Euro Surveill. 2013;18(32):pii=20552. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20552

Article submitted on 17 September 2012 / published on 08 August 2013

In 2007 in Navarre, Spain, universal varicella vaccination with two doses of Varivax was introduced in the childhood immunisation schedule for children aged 15 months and three years. This study describes changes in the epidemiology of varicella in the period 2006 to 2012 and evaluates vaccination effectiveness using epidemiological surveillance data. The incidence of varicella in children aged 0 to 14 years decreased by 98.1%, from 50.1 cases per 1,000 inhabitants in 2006, to 1.0 per 1,000 in 2012. Children aged one to eight years were the vaccinated cohorts, and their incidence of varicella decreased by 98.5% (p<0.0001). In unvaccinated age groups, important reductions were also achieved between 2006 and 2012: 90.5% (p<0.0001) in infants under one year of age, and 89.4% (p<0.0001) in children aged nine years. In the period 2006 to 2012, the hospital admissions rate for varicella or its complications decreased by 89.0%, and in 2012, there was only one admission of a newborn with neonatal varicella. Vaccine effectiveness for at least one dose was 96.8% (95% confidence interval: 96.3-97.2%). Universal vaccination with two doses has reduced varicella circulation to minimum levels within five years and has proved highly effective.

Introduction

In the absence of vaccination, varicella-zoster virus (VZV) circulates widely and infects most people during childhood [1]. Varicella typically occurs during the school year, with outbreaks affecting classmates and family members [2-5]. In 1995 the first varicella vaccine, with one dose, was introduced in the childhood vaccination schedule in the United States (US). Subsequent years saw a reduction, not only of cases of varicella, but also of hospitalisations due to its complications [6-8]. In other countries like Australia [9,10], Germany [11] and Italy (Region of Veneto) [12], universal childhood vaccination against varicella has had similar effects.

Despite high one-dose vaccination coverage and the success of the vaccination programme in the US, the occurrence of continued outbreaks in highly vaccinated populations and an increasing number of vaccine failures [8,13] led the Advisory Committee on Immunization Practices (ACIP) in 2006 to recommend a second dose of the vaccine [4]. The two-dose scheme is expected to have a rapid and pronounced impact on the control of varicella circulation [14].

Thanks to herd immunity, varicella vaccine protects not only those who are vaccinated, but also the unvaccinated, since the probability that susceptible individuals will come into contact with the VZV diminishes [15,16]. This indirect effect could also contribute to the impact of a universal varicella vaccination programme. Most studies have evaluated the impact of varicella vaccination programmes which started with a single-dose scheme or which introduced the second dose after a period of using a one-dose programme. It would be interesting to have evidence on the potential impact of the introduction of varicella vaccination in childhood with a two-dose scheme.

Navarre is a Spanish region with 644.566 inhabitants in 2012, of whom 100.282 were under 15 years-old. The Navarre Health Service provides healthcare, free at point of service, to 97% of the population; it comprises one tertiary hospital in the main city, two small local hospitals, all of them with paediatric wards and emergency rooms, and 54 primary healthcare centres. The clinical reports have been computerised since 2000, and include those from both primary care and hospital admissions. All vaccine doses administered are registered at the vaccination points.

In 2004, Navarre began varicella vaccination for all susceptible individuals (individuals with no history of varicella and who had not been previously vaccinated) at age 14 years for cohorts born since 1990. In 2006, the age of vaccination of susceptible children was lowered to 10 years for all those born since 1996. A school catch-up vaccination was performed for susceptible persons born between 1992 and 1995. In 2007,

universal vaccination with two doses was introduced for all children born since 2006. The schedule calls for the first dose of vaccine at the age of 15 months and a second dose at the age of three years. In order to obtain a rapid decrease in varicella cases, all children born in 2004 and 2005 were offered vaccination with one dose at the age of three years. In addition, vaccination of susceptible individuals continued for all children who had not received universal vaccination (those born between 1996 and 2003). In 2011, a second dose of vaccine was offered to all cohorts who had previously received only one dose.

Varicella and measles-mumps-rubella vaccinations in Navarre are administered at the same time, but in separate vaccines. Varilrix was used for vaccination of susceptible adolescents until the end of 2006, and Varivax was used for all vaccinations after that. In the period from 2009 to 2012, vaccination coverage was around 95% for the first and second doses of measles-mumps-rubella vaccine and the first varicella vaccine dose, and over 89% for the second varicella vaccine dose (data not shown).

The aim of this study is to describe the epidemiology of varicella in Navarre, Spain, since the introduction of universal vaccination with a two-dose scheme, in terms of its impact on both vaccinated cohorts (direct effect) and unvaccinated cohorts (indirect effect), and to assess the vaccine effectiveness.

Methods

Study design and information sources

Varicella is a notifiable disease in Navarre [17]. From the electronic clinical reports of primary healthcare, automatic notification of all diagnoses of varicella (ICPC-2 code A72) is generated according to the International Classification of Primary Care, Second Edition (ICPC-2) [18], including the date of consultation, date of birth, sex and vaccination history.

Varicella surveillance in hospitals is conducted by trained nurses, who review clinical and laboratory reports daily to search for cases among admitted patients. At the end of each year this information is validated with hospital discharge diagnoses. In the present study, we considered all admissions with a principal diagnosis of varicella (ICD-9 code 052.9) or complication of varicella (ICD-9 codes 052.0, 052.1, 052.7, 052.8) according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [19]. A unique patient identification number was used to detect and exclude duplicate cases. The number of vaccine doses received, the date and the brand name were taken from the regional vaccination registry.

In the cohorts of vaccinated children, three possible explanations for cases of varicella were considered according to the temporal criteria already described [20]: Cases with onset in the first 14 days after the first vaccine dose were considered as not related to the vaccine; those occurring between 15 and 42 days after receipt of a vaccine dose were attributed to the vaccine virus, and all cases occurring more than 42 days after administration of a dose of varicella vaccine were considered vaccine failures or breakthrough varicella.

Statistical analysis

To calculate incidence rates, we used as the denominator the population of Navarre at the beginning of each year, according to the National Statistics Institute [21] of Spain. To assess the impact of vaccination, we compared the incidence in 2012 with the incidence in 2006, the year before universal vaccination was initiated. We

Figure 1

Notified varicella cases, by four-week period, Navarre, 2006–2012 (n=10,477)

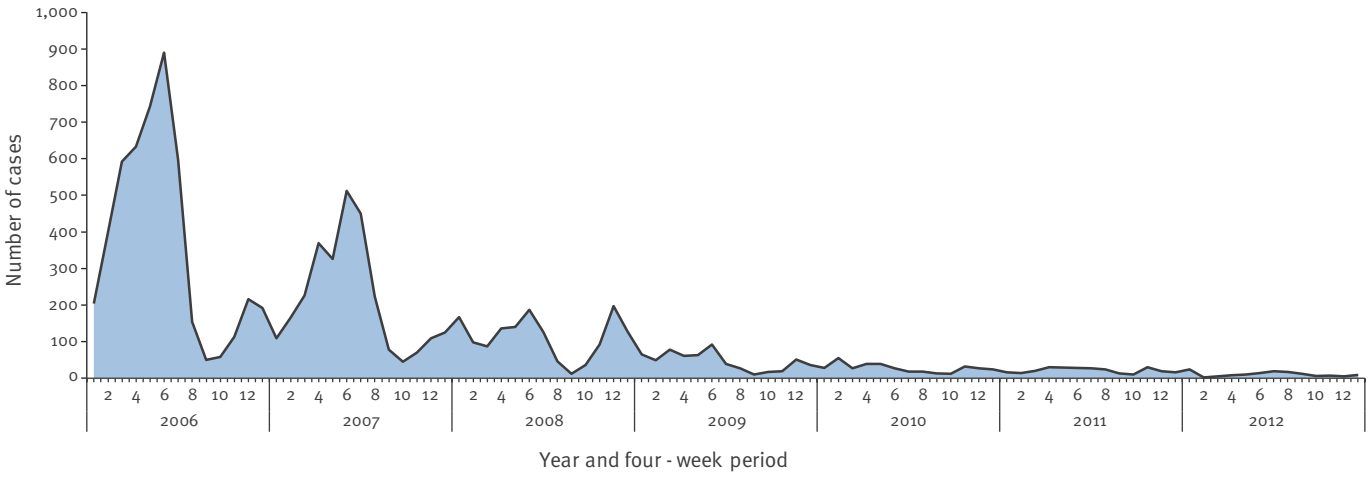
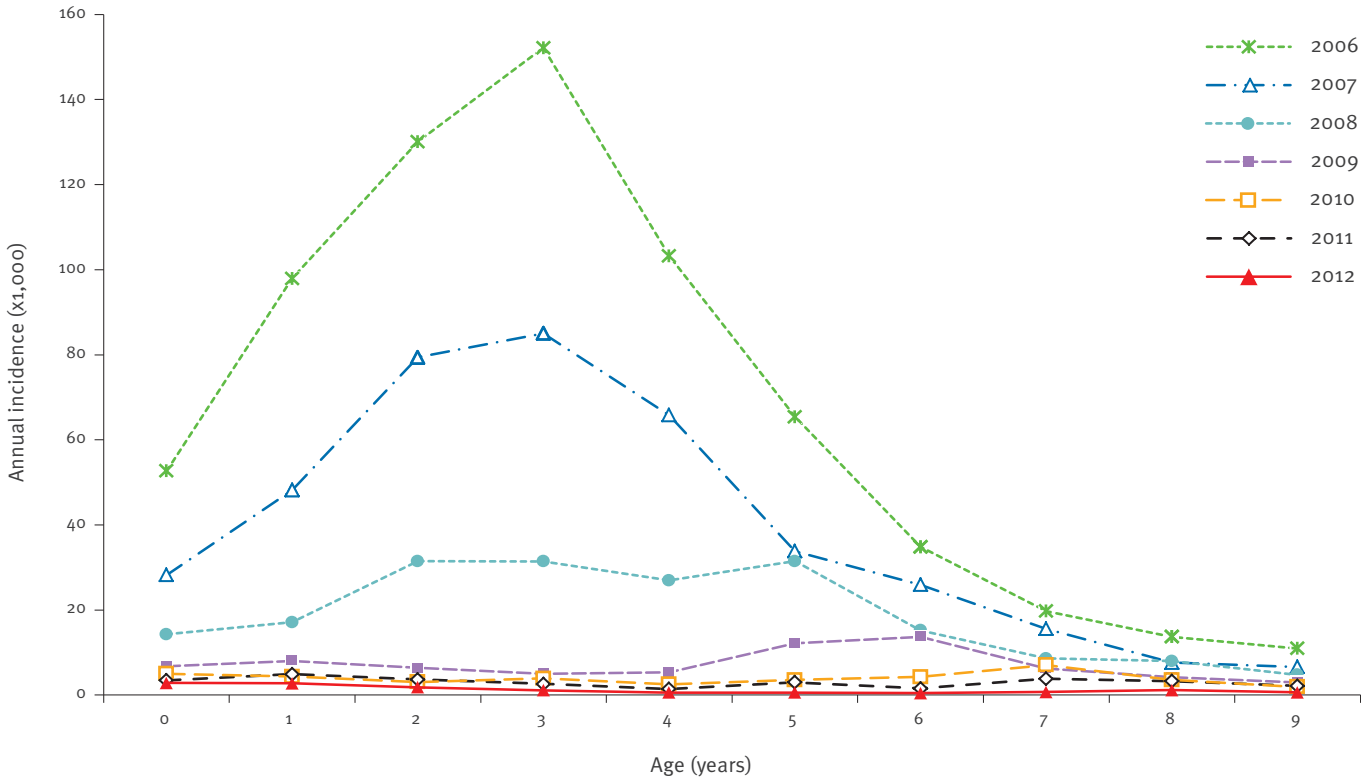


Figure 2

Annual incidence of varicella per 1,000 inhabitants by age, Navarre, 2006–2012



evaluated the direct effect of vaccination in age groups in which universal vaccination was offered, and the indirect effect (herd immunity) in unvaccinated age groups. The chi-square test and Fisher's exact test were used for the statistical analysis.

Varicella vaccine effectiveness for at least one dose was calculated using the screening method proposed by Farrington [22], based on a comparison of the proportion of vaccinated persons among the cases and the population. Vaccine effectiveness (VE) is then given by the expression:

$$VE = 1 - \left[\frac{PCV}{(1 - PCV)} \times \frac{(1 - PPV)}{PPV} \right]$$

where PCV is the proportion of cases vaccinated and PPV is the proportion of the population vaccinated. We estimated vaccine effectiveness in the birth cohorts born between 2004 and 2010 that had received the vaccine between 2007 and 2012.

Results

Figure 1 shows the time trend of varicella incidence in Navarre in 2006 to 2012. Of note is the marked seasonality in the first years, with peaks in late spring, and a rapid reduction in incidence during the study period.

Incidence of varicella

From 2006 to 2012, 10,477 cases of varicella were diagnosed in primary healthcare, 50.7% in males, 62.5% in children under five years-old, and 87.6% in those younger than 15 years. The incidence of varicella decreased progressively, from 8.04 cases per 1,000 inhabitants in 2006 to 0.21 per 1,000 in 2012, a reduction of 97.3% ($p<0.0001$). The incidence of varicella in children aged 0 to 14 years decreased from 50.1 cases per 1,000 inhabitants in 2006 to 1.0 cases per 1,000 in 2012, which represented a 98.1% reduction.

While 82.9% of cases occurred in children under age 15 in 2006, this percentage decreased to 70.3% in 2012. Furthermore, the peak incidence of varicella have moved, from the three year-olds in 2006 to a situation with two small peaks in 2012, corresponding to children under 15 months-old and children aged nine years, as these children have not yet been vaccinated (Figure 2).

Impact of varicella vaccination

In children aged one to eight years, the cohorts vaccinated in the universal vaccination programme, the incidence of varicella decreased by 98.5% ($p<0.0001$). Important reductions were also observed in cohorts vaccinated at age 10 to 21 years. The incidence declined by 93.8% ($p<0.0001$) among the 10 to 16 year-olds and

Table 1

Annual incidence of varicella per 1,000 inhabitants among age groups included in universal vaccination (1–8 years) and vaccination of susceptibles (10–21 years), Navarre, 2006–2012

Age groups	2006	2007	2008	2009	2010	2011	2012	% reduction 2006–2012
Universal vaccination								
1 year	70.1	32.8	19.2	8.5	5.3	5.1	2.9	95.9%[c]
2 years	117.9	67.3	11.3	7.3	3.8	3.6	2.7	97.7%[c]
3 years	133.0	78.0	46.7	5.2	3.6	3.5	1.4	99.0%[c]
4 years	142.8	86.3	15.3	5.4	3.3	1.3	0.7	99.5%[c]
5 years	94.9	49.3	43.0	4.5	2.8	2.2	0.3	99.7%[c]
6 years	51.7	30.0	21.4	21.7	3.5	2.5	0.7	98.6%[c]
7 years	28.3	19.7	9.5	7.4	6.3	1.6	0.3	99.0%[c]
8 years	14.4	12.5	9.8	5.2	5.9	5.0	0.7	94.9%[c]
Total 1–8 years	**92.1**	**52.6**	**23.9**	**8.5**	**4.1**	**2.8**	**1.2**	**98.5%[c]**
Vaccination of susceptibles								
10–16 years[a]	**7.3**	**2.0**	**1.6**	**1.5**	**0.6**	**0.4**	**7.3**	**95.6%[c]**
17–21 years[b]	**2.7**	**1.4**	**0.6**	**0.6**	**0.4**	**0.2**	**0.3**	**90.1%[c]**

[a] Vaccinated at 10 years of age.
[b] Vaccinated at 11, 12, 13 or 14 years of age.
[c] p value <0.001.

by 90.1% (p<0.0001) in persons aged 17 to 21 years (Table 1).

Also in unvaccinated age groups, important reductions were achieved between 2006 and 2012: 90.5% (p<0.0001) in infant under the age of one year, and 89.4% in nine-year old children. In people older than 21 years, the overall reduction was 92.4% (p<0.0001) (Table 2).

Before the introduction of universal vaccination, most cases (77.7%) occurred in winter and spring, with a peak in weeks 21 to 24 (second half of May to first half of June). A slight change in the seasonality of varicella was observed, in that in 2012, only 52.2% of cases occurred in that period. Moreover, due to an overall reduction in varicella incidence, cases in 2012 were distributed more homogeneously throughout the year, especially from autumn to spring.

Varicella in vaccinated individuals and breakthrough varicella

Between January 2007 and March 2013, 42,860 children born between 2004 and 2011 were vaccinated against varicella: 14,617 received only one dose and 28,243 had two doses. In these birth cohorts, 2,448 cases of varicella were diagnosed until December 2012, 260 of which (10.6%) occurred in vaccinated children. Considering the time interval between the last dose and symptom onset, 22 cases were considered to be vaccine cases (0.9%) and 238

Table 2

Annual incidence of varicella per 1,000 inhabitants in unvaccinated age groups (indirect effect), Navarre, Spain, 2006–2012

Age groups	2006	2007	2008	2009	2010	2011	2012	% reduction 2006–2012	p
< 1 year	**12.5**	**8.7**	**5.5**	**1.9**	**1.5**	**1.3**	**1.2**	**90.5%**	**<0.0001**
9 years	**11.7**	**6.3**	**5.9**	**3.0**	**2.4**	**2.9**	**1.2**	**89.4%**	**<0.0001**
22–24 years	1.6	1.2	0.6	0.4	0.3	0.1	0.1	96.8%	<0.0001
25–44 years	1.6	0.9	0.6	0.3	0.2	0.2	0.05	92.4%	<0.0001
45–64 years	0.2	0.2	0.1	0.08	0.06	0.07	0.04	84.6%	0.0015
≥65 years	0.1	0.07	0.04	0.03	0.02	0.02	0.01	91.7%	0.0526
Total ≥22 years	**0.8**	**0.5**	**0.3**	**0.2**	**0.1**	**0.1**	**0.06**	**92.4%**	**<0.0001**

Table 3

Hospital admissions with diagnosis of varicella (ICD-9-CM code 052.9) and varicella with complication (ICD-9-CM codes 052.0, 052.1, 052.7 and 052.8), Navarre, Spain, 2006–2012 (n=71)

	2006	2007	2008	2009	2010	2011	2012	% reduction 2006–2012
Total population								
Hospital admissions	25	22	11	7	1	2	3	88%
Average stay (days)	5.9	5.0	3.4	5.0	6.0	1.5	4.3	NA
Admissions per 100,000	4.2	3.6	1.8	1.1	0.3	0.3	0.5	89%[a]
Number of complicated varicella	10	10	2	3	0	0	0	NA
Children <15 years								
Hospital admissions	18	14	9	2	0	0	1	94%
Average stay (days)	5.9	4.6	3.2	4.0	NA	NA	3,0	NA
Admissions per 100,000	20.9	15.9	9.9	2.1	0	0	1,0	95%[a]
Number of complicated varicella	5	6	1	1	0	0	1	NA

NA: not applicable.

[a] p value =0.0001.

as vaccine failures or breakthrough varicella (9.7%). One medical consultation for varicella attributable to the vaccine virus was produced for every 3,231 doses administered: one consultation for every 2,381 first doses, and one for every 7,060 second doses. About 82% of vaccine-attributable cases of varicella occurred after administration of the first dose.

Among the 42,860 vaccinated children, 238 cases of breakthrough varicella were diagnosed (0.56%). About 85% of vaccine failures (n=202) occurred after administration of the first dose, corresponding to 1.38% of those vaccinated with one dose), while 36 vaccine failures occurred after the second dose (0.13% of those vaccinated with two doses; p<0.0001). One medical consultation for breakthrough varicella was produced for every 299 doses administered: one consultation for every 212 first doses, and one for every 785 second doses.

Hospitalisations due to varicella

The incidence rate of hospitalisations for varicella declined by 89%, from 4.2 per 100,000 inhabitants in 2006 to 0.5 per 100,000 in 2012 (p<0.0001). In children under 15 years the rate declined by 95%, from 20.9 to 1.0 per 100,000 (p<0.0001), with only one hospitalisation of a newborn with neonatal varicella (Table 3).

Effectiveness of varicella vaccine

Between 2007 and 2012, 36,971 of the 47,908 children born between 2004 and 2010 had received at least one dose of varicella vaccine (77.2%). In the same period, 2,422 cases of varicella were diagnosed in children

Table 4

Estimated vaccine effectiveness of any dose of varicella vaccine in vaccinated cohorts (children born between 2004 and 2010), Navarre, 2007–2012

Birth year	Population			Varicella cases			Vaccine effectiveness (95% confidence interval)	
	n	Vaccinated n (%)		n	Vaccinated n (%)			
2004	6,723	2,357	(35)	678	19	(3)	94.7	(91.6–96.6)
2005	6,612	3,104	(47)	819	23	(3)	96.7	(95.1–97.8)
2006	6,869	6,004	(87)	355	86	(24)	95.4	(94.2–96.3)
2007	6,881	6,207	(90)	271	47	(17)	97.7	(96.9–98.3)
2008	7,135	6,587	(92)	147	29	(20)	98.0	(97.0–98.6)
2009	6,917	6,434	(93)	87	24	(28)	97.1	(95.5–98.2)
2010	6,771	6,278	(93)	65	10	(15)	98.6	(97.2–99.3)
2004–2010	**47,908**	**36,971**	**(77)**	**2,422**	**238**	**(10)**	**96.8**	**(96.3–97.2)**

born between 2004 and 2010, and 238 of these cases had previously been vaccinated (9.8%). Accordingly, the effectiveness of at least one dose of varicella vaccine was 96.8% (95% confidence interval: 96.3–97.2%). Table 4 shows the effectiveness for each birth cohort, which ranged from 94.7% to 98.6%.

Discussion

Universal varicella vaccination with a two-dose scheme has greatly reduced the impact of this disease in the whole population of Navarre. The reduction was particularly great in the vaccinated cohorts of children aged one to eight years, with a 98.5% decline in incidence within a period of only five years, higher than that reported in other places where universal vaccination has been introduced, such as the US and the Veneto region in Italy [6,12,23-25]. An important reduction in varicella incidence was also noted in persons aged 10 to 21 years, in cohorts included in the strategy of vaccination of susceptibles. Such marked declines may be explained by the introduction of universal vaccination with two doses from the beginning, and the high coverage achieved since the first year.

Varicella incidence also decreased considerably in the unvaccinated cohorts, especially in infants under the age of one year (90.5%), which can be attributed to a herd immunity effect due to reduced circulation of VZV [16]. In children aged nine years and persons over the age of 21 years, significant reductions are also noted, whereas the impact in older adults was lower given that the incidence of the disease in this group had already been low before. All these changes have led to a slight forward shift in the age pattern of this disease. The proportion of cases under 15 years-old have declined, and the peak incidence, which typically occurred at the age of three years, has shifted to the age groups not yet vaccinated, and is now much less pronounced than before.

Rates of hospitalisation for varicella declined markedly (88%), more pronounced and quickly than reported in other countries [7,26-28]. In children under the age of 15 years, there was only one hospitalisation in 2012, showing that vaccination has had a substantial impact in reducing severe and complicated forms of varicella.

Because it contains attenuated virus, the varicella vaccine may infrequently cause disease, generally mild, in immunocompromised individuals, although cases have also been described in immunocompetent people [29]. From an epidemiological perspective, only 0.9% of cases of varicella in vaccinated individuals in our study were attributable to the vaccine virus, given that they appeared between 14 and 42 days after vaccine administration.

We observed vaccine failures in children with one and two doses of varicella vaccine, although these cases were generally not confirmed by laboratory. Breakthrough disease can be difficult to accurately diagnose clinically and may be overreported in the absence of laboratory confirmation [14]; we defined it as a case of varicella that appears in a person who was vaccinated more than 42 days before the onset of symptoms. Other authors have reported that these cases typically exhibit a shorter duration of illness, fewer constitutional symptoms, less than 50 skin lesions, and a rash that may show an atypical appearance (maculo-papular with few or no vesicles) [20,30]. However, breakthrough disease also results in medical consultation and can transmit the virus to susceptible individuals, which may lead to outbreaks [20,25].

The need for a second dose of vaccine has been widely assessed. Brisson et al. estimated that protection wanes by up to 3% per year, with the consequent risk of developing a breakthrough infection if exposed to VZV [31]. As has been suggested, a second dose offers additional protection and reduces the possibility of breakthrough cases [25,32-34]. Our approach to vaccine effectiveness in vaccinated cohorts showed high effectiveness (96.8%) in a programme where most of children had received two doses. One study estimated that vaccine efficacy after a 10-year follow-up was 94.4% for one injection and 98.3% for two injections [35]. Shapiro et al. have estimated that the odds of developing varicella were 95% lower for children who received two doses than for those who received one dose of varicella vaccine in the first 2.5 years after recommendation of a routine second dose in the US vaccination programme [25].

The main limitation of the present study is its ecological design and the fact that it is based on epidemiological surveillance data. The incidence of varicella in the population usually varies over time, but the marked reductions in incidence following the introduction of the vaccine would be difficult to explain by other causes. Varicella surveillance in Navarre during the study period was based on automatic notification from electronic clinical reports, which were fully implemented throughout the healthcare network, making underreporting of cases highly unlikely and ensuring a high level of completeness of information.

Immunity to VZV might be maintained by external boosting of immunity through exposures to varicella or herpes zoster [36]. Exposure to varicella might reduce the risk of zoster [37,38] and on the other hand, its absence would lead to an increase of herpes zoster [34,39]. Although this possible negative effect of the two-dose universal vaccination programme has not been taken into account in this study, recent studies have not demonstrated a relationship between varicella vaccination and increase of zoster disease in the general population [20,40,41]. Moreover, others have reported a reduction in zoster incidence in vaccinated [40,42]. In this context of universal varicella vaccination, long-term studies to monitor zoster incidence will be necessary to assess whether zoster rates increase.

This study was based on clinically diagnosed cases of varicella, which were only occasionally confirmed by laboratory. The clinical diagnosis of varicella is highly specific in the context of wide virus circulation in the population. However, in situations of very low incidence, other diseases with clinical features similar to varicella, although infrequent, may acquire appreciable weight relative to the clinical diagnoses of varicella. In order to maintain a high specificity in varicella diagnosis, it may be desirable to incorporate virological confirmation of varicella cases in populations with high vaccination coverage, especially in breakthrough cases, since, in the absence of a large number of vesicles, they might be confused with other viral syndromes.

In conclusion, five years after the inclusion of two doses of varicella vaccine in the childhood vaccination schedule of Navarre, the incidence of this disease has diminished drastically, not only in vaccinated individuals, but also in the unvaccinated, due to herd immunity. Hospital admission rates are also lower. Varicella vaccine has been shown to be highly effective. In this situation of very low incidence, it is very important to continue varicella surveillance and to assess disease trends over time; laboratory confirmation of varicella cases is also recommended.

Acknowledgements

This work has been funded by the Health Department of the Regional Government of Navarre (Project 77/09) and by the Spanish Ministry of Health and Social Services (EC11-308).

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Systematic review of tattoo-associated skin infection with rapidly growing mycobacteria and public health investigation of a cluster in Scotland, 2010

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Citation style for this article:
Conaglen PD, Laurenson IF, Sergeant A, Thorn SN, Rayner A, Stevenson J. Systematic review of tattoo-associated skin infection with rapidly growing mycobacteria and public health investigation of a cluster in Scotland, 2010. Euro Surveill. 2013;18(32):pii=20553. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20553

Article submitted on 06 July 2012 / published on 08 August 2013

Sporadic cases and outbreaks of tattoo-associated skin infection with rapidly growing mycobacteria have been reported although they often contain few details of public health investigations and have not previously been systematically collated. We present the details of the public health investigation of a cluster of cases, which occurred in Scotland in 2010. Investigation of the cluster involved case finding, environmental investigation of the tattoo studio and pathological and microbiological investigation of possible cases and tattoo ink. *Mycobacterium chelonae* was isolated from one case and three probable cases were identified. *M. chelonae* was grown from an opened bottle of ink sourced from the studio these cases had attended. In addition, in order to identify all published cases, we conducted a systematic review of all reported cases of tattoo-associated skin infection with rapidly growing mycobacteria. A total of 25 reports were identified, describing 71 confirmed and 71 probable cases. Mycobacteria were isolated in 71 cases and *M. chelonae* was cultured from 48 of these. The most frequently postulated cause of infection was the dilution of black ink with tap water. Reports of tattoo-associated rapidly growing mycobacterial skin infection are increasing in frequency. Interested agencies must work with the tattoo industry to reduce the risk of contamination during tattoo ink manufacture, distribution and application.

Introduction

Rapidly growing mycobacteria (RGM) are a non-tuberculous group of mycobacteria commonly found in the environment in water, soil and dust [1]. The incidence of human infection with RGM is poorly described [2] although an increasing literature of sporadic cases and outbreaks has established RGM as important opportunistic human pathogens in both immunocompromised and healthy individuals [3]. RGM can cause a wide variety of conditions including catheter infections, skin and soft tissue infection, respiratory, endocardial, meningeal or bone infection and disseminated disease [2].

In recent years, tattooing has become increasingly popular [4]. Both the peer-reviewed and grey literature contain sporadic reports of cases and outbreaks of RGM skin infection associated with tattooing [5-29]. Contamination leading to such tattoo-associated infection could theoretically occur at any point, from manufacture of the tattoo ink or equipment to application of the tattoo in the studio or during aftercare of the tattoo by the recipient. Reports of this emerging condition often contain few details of the public health investigations into the potential points of contamination and these reports have not previously been systematically collated.

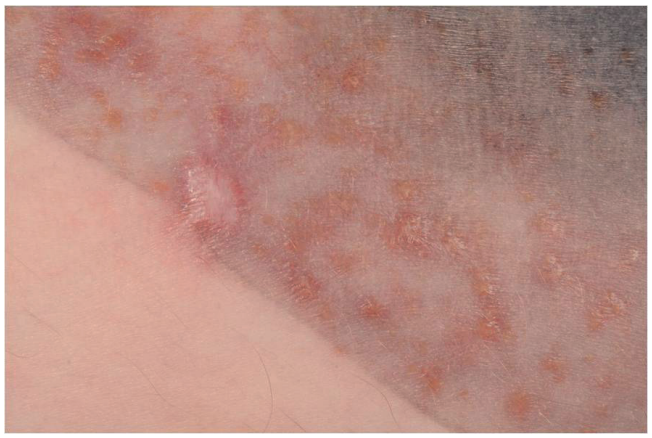
A recent report described the clinical investigation and treatment of the United Kingdom's (UK's) first confirmed case, and three probable cases, of tattoo-associated RGM skin infection, which occurred in Scotland in 2010 [23]. Full details of the clinical investigation and treatment of these cases can be found in the original report [23]. In brief, the presentation and findings were similar for all four patients: within two weeks of their most recent tattoo session, erythematous papular eruptions appeared, predominantly in the grey-shaded areas of their tattoos (Figure 1). Histopathology suggested an infectious aetiology in each case although the Scottish Mycobacteria Reference Laboratory only isolated an organism (*M. chelonae*) from the skin biopsy of one of the four individuals. All four had received their tattoos from a single tattooist at the same tattoo studio in Edinburgh between August and September 2010. The four individuals demonstrated initial spontaneous improvement; all were lost to subsequent follow-up [23].

We present a detailed description of the public health investigation of this cluster of cases of tattoo-associated

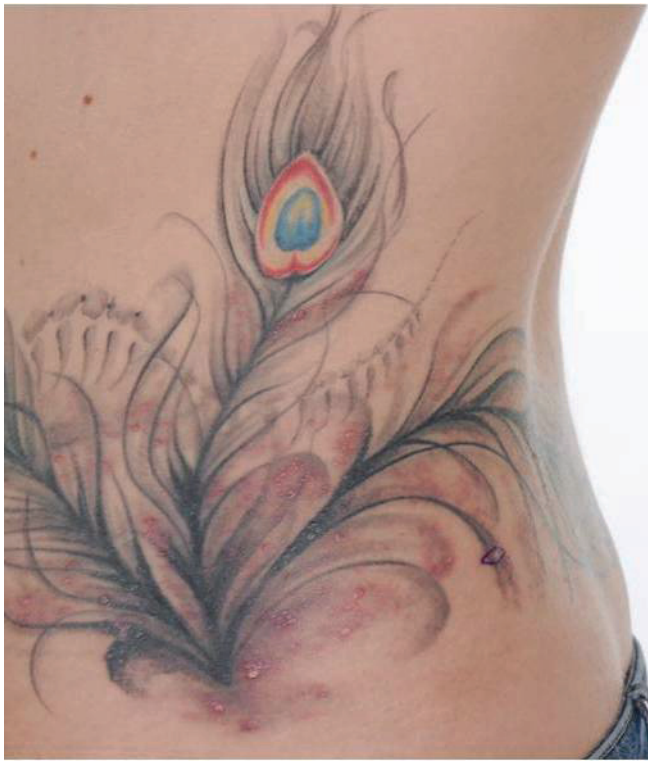
Figure 1

Lesions caused by tattoo-associated skin infection with rapidly growing mycobacteria from a cluster of one confirmed and three probable cases, Scotland, 2010

A



B



A Healing lesions localised in the grey-shaded areas of the confirmed case's tattoo. The skin biopsy site is also visible.

B Erythematous papular eruptions within the tattoo of one of the probable cases.

RGM skin infection in Scotland alongside a systematic review of all such cases reported in the literature.

Methods

Public health investigation into a cluster of tattoo-associated rapidly growing mycobacteria skin infection in Scotland

Case definition

Our initial case definition was any individual within the Lothian region of Scotland who, in the 12 months preceding the investigation, had RGM isolated from a recently tattooed area of skin. Recently tattooed was defined as tattooed in the 12 months before symptom onset. Patients from whom RGM were not isolated, but who had a clinical picture consistent with RGM skin infection in a recently tattooed area of skin, were defined as possible cases.

After initial case finding, the following final case definitions were agreed:

- confirmed case – a patient with clinical signs consistent with RGM skin infection (e.g. erythema, papules or pustules) in or around a recently tattooed area and from whom RGM were isolated;
- probable case – a patient with clinical signs from whom RGM were not isolated but who had an epidemiological link to a confirmed case (e.g. attended the same tattoo studio).

Case finding

The first case presented to his general practitioner (GP) in October 2010 and was referred to NHS Lothian, Department of Dermatology in January 2011. Having noticed other cases with a similar history, dermatology colleagues notified the local Public Health team in March 2011. Further cases were then sought by reviewing medical photography records for tattoo-associated lesions with similar characteristics between October 2010 and March 2011 and by searching the Scottish Mycobacteria Reference Laboratory records for cases of RGM infection associated with tattoos between January 2009 and March 2011.

An enhanced surveillance notification form was developed for local dermatologists to complete on seeing any tattoo-associated lesions. Organisations that might become aware of tattoo-related infections were contacted and asked to report any similar cases. These included: local authority liaison groups, the Scottish Skin Piercing Working Group, Health Protection Scotland, the former Health Protection Agency and the Health Protection Team at Christchurch Borough Council, Dorset (where the tattoo ink distributor was based).

Environmental investigation

The local tattoo licensing authority, City of Edinburgh Council, investigated the tattoo studio. Further to previous routine inspections, a visit was conducted that

inspected the tattoo studio and its practices. A number of bottles of tattoo ink and diluent were obtained from both the tattoo studio (opened bottles) and directly from their distributor (unopened bottles) and sent for microbiological analysis. As the environmental investigation was conducted in March 2011, six to seven months after the tattoos were applied, the samples tested would not have been from ink used to tattoo the cases.

Microbiological investigation

Environmental samples were investigated by Edinburgh Scientific Services and the Scottish Mycobacteria Reference Laboratory in Edinburgh and also the former Health Protection Agency Food Water and Environmental Microbiology Laboratory in Southampton. Samples included tattoo ink, diluent and washings from an ink-bottle nozzle.

Literature review

A literature search was conducted to identify all articles describing new confirmed cases of RGM skin infection associated with tattooing. The final case definitions listed above were used to classify confirmed and probable cases. Where a report also included details of probable cases, these were noted.

The initial search (last updated on 1 February 2013) used the controlled vocabulary terms 'Tattooing' AND 'Mycobacterium' within MEDLINE and Embase, combined with free-text searches for 'tattoo*' AND 'mycobacter*' in the same databases and in Web of Science. Searches were conducted using all available records within each database: up to November 2012 (MEDLINE) and December 2012 (Embase and Web of Science), without language restrictions. Duplicate records were discarded. Titles and abstracts were screened to identify articles that could confidently be excluded (see below). Full-text review of the remaining articles allowed inclusion/exclusion of publications, as per the criteria described below.

The reference lists of included publications were visually scanned for any further relevant titles. A Google Scholar search was conducted on 2 February 2013 for 'Tattoo mycobacter' with no language restrictions, using the inclusion/exclusion criteria described below. The title and preview text of each result on the first 20 pages of Google Scholar search results were visually scanned, to identify further cases from the grey literature.

The inclusion criteria were that the report contained at least one confirmed case of RGM skin infection – i.e. a patient with consistent clinical signs (see above), in or around a recently tattooed area (tattoo applied within 12 months of presentation, if stated), from whom RGM were isolated.

Reports were excluded if they did not contain a confirmed case, if they were review articles that only described previously published cases or if they were preliminary reports (e.g. conference abstracts) that were later published in full (e.g. a peer-reviewed article). Where necessary, authors were contacted to confirm such duplication. To reduce the burden of full-text retrieval and review, records were excluded if initial review of the title and abstract clearly identified a report containing only non-RGM infection (e.g. *M. tuberculosis*), a report containing only non-infectious cases (e.g. those with sarcoidosis) or a non-clinical study.

Results

Public health investigation into a cluster of tattoo-associated rapidly growing mycobacteria skin infection in Scotland

Case finding

As reported by Sergeant et al. [23], four cases were identified who met the case definition (one confirmed case and three possible cases). Neither enhanced surveillance nor awareness-raising exercises with other agencies led to the identification of any further cases. Analysis of six months of consent forms from the tattoo studio identified that they tattooed a mean of 133 clients per month. The four cases who attended this studio over two months thus represented 3% (95% confidence interval (CI): 1–8) of the clients who would have attended the studio during this period.

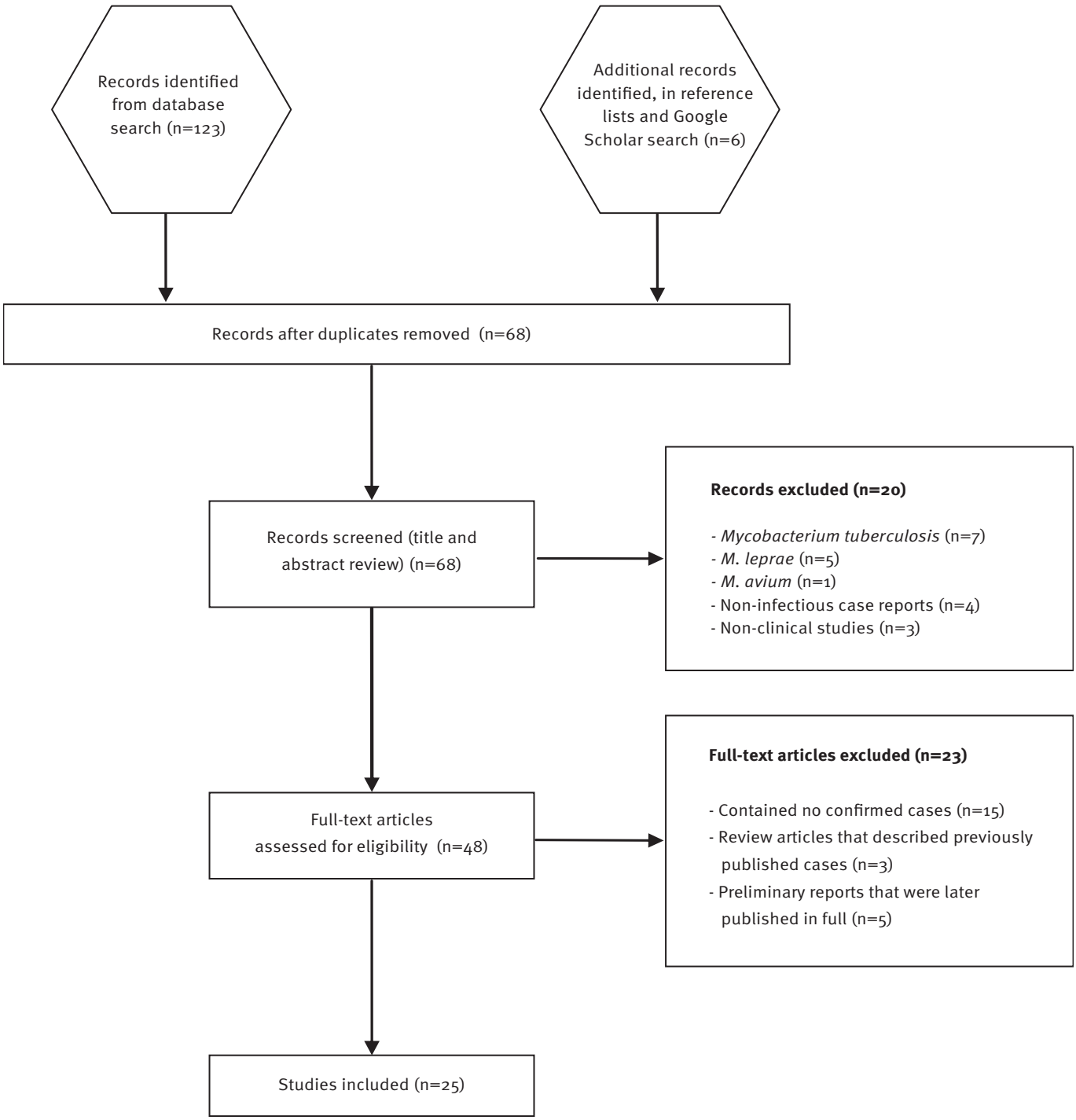
Ink and diluent samples

Edinburgh Scientific Services conducted microbiological analyses on samples from four opened bottles of tattoo ink from the studio (two black and two grey), which identified *Cupriavidus pauculus* in the sample from one bottle of grey ink. Like *M. chelonae*, *C. pauculus* is a common environmental organism found, among other places, in tap water and is seldom isolated from clinical samples [30]. While this finding was unlikely to have any clinical relevance, it indicated that this opened bottle was not sterile. The opened bottle of grey ink that had produced this sample was retrieved from the studio along with a further two opened bottles of the same brand of ink and one opened bottle of diluent of the same brand. The studio had no unopened bottles of this brand. Samples from these four opened bottles were sent to the Scottish Mycobacteria Reference Laboratory, who subsequently isolated *M. chelonae* from the bottle sample that had originally grown *C. pauculus*. No microorganisms were identified in samples from the other three bottles.

In an attempt to identify the likely source of contamination, four unopened bottles of ink were obtained from the UK-based distributor, which supplied the studio with this American brand of ink. Samples were sent to the respective local authority laboratories and to the Scottish Mycobacteria Reference Laboratory. No

Figure 2

Flow chart showing the selection of articles in the literature review to identify new cases of tattoo-associated skin infection with rapidly growing mycobacteria



organisms were identified from any of the unopened bottles of ink from the distributor.

Environmental investigation

The tattoo studio's practices, premises and equipment all met local authority licensing requirements on both the investigative visit and during previous routine inspections. Specifically, the studio used ready-to-use inks that bore an indication of durability (or 'use before' date). Their grey inks were purchased premixed and the tattoo artist stated that he had not diluted them with tap water in the studio. Tattoos were applied using aliquots of ink decanted into small single-use sterile pots.

Some UK distributors of tattoo inks are known to have their products sterilised by industrial gamma irradiation after import. The distributor that supplied this studio with the brand of ink under investigation did not.

Control measures

The tattoo studio voluntarily agreed to remove this brand of ink from use while the investigation was ongoing. An alert letter, detailing the brand and batch of ink was sent to all tattoo studios in the Lothian region, recommending it be withdrawn from use as a precaution. The UK distributor that supplied this brand of ink to the studio was also informed.

Investigation outcome

At the conclusion of our investigation, we had identified one confirmed case. While no microorganism was isolated from the three possible cases, the combination of clinical, pathological and epidemiological similarities was highly suggestive of a small cluster and these three cases were reclassified as probable cases. The exact source of the contamination was not identified.

Literature review

A flow chart of the selection of articles in the literature review can be seen in Figure 2. Our MEDLINE and Embase search identified 62 unique publications after the removal of 61 duplicate records. Title and abstract screening allowed the exclusion of 20 reports that did not meet inclusion criteria. Review of the titles of articles in the references of the remaining 42 articles identified two further reports and a Google Scholar search identified an additional four. From these 48 articles, 15 were excluded which contained no confirmed cases; three were excluded as review articles which described previously published cases and five were excluded as preliminary reports, which were later published in full. Interested readers may wish to note the research letter by Kluger et al. (which was excluded from this review as it contains no confirmed cases) as it gives a thorough account of a probable outbreak [31]. The report of an outbreak of seven cases in Germany by Hamsch et al. was included as, in two of the cases, DNA of an atypical mycobacterium that had not previously been described was detected by polymerase chain reaction (PCR) – it bore features of *M. haemophilum* [14].

We identified a total of 25 reports that describe new cases of tattoo-associated RGM skin infection. These are summarised in the Table. The literature review identified the report of an outbreak in Rochester in New York State, United States, published by Kennedy et al. in August 2012 [24]. This outbreak was also summarised in an article in the Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly Report*, which provided preliminary descriptions of four further clusters (not published elsewhere) that were identified as part of a subsequent, national investigation [25]. For the purposes of this review, the Kennedy et al. report was selected for the Rochester cases (as it contains full details) and the CDC article was selected as a separate single report of the remaining four clusters (with the Rochester cases excluded, to avoid duplication).

The 25 reports analysed, from 11 countries, described a total of 142 cases (71 confirmed and 71 probable cases). Three of the reports described infections following the application of 'permanent make-up' [14-16]. The techniques used for this cosmetic form of tattooing are broadly similar to conventional tattooing although the pigment tends to be applied more superficially [14,32].

The number of published cases by year of publication is shown (Figure 3). In the six years following the first reported case in 2003, there were only three reports of such infections. However, the last three years (2010–2012) have seen a large rise both in the number of annual reports and in cumulative count of cases.

There are many similarities in the clinical presentation of reported cases, with descriptions tending to include erythema, nodules, papules or pustules usually confined to or around the tattooed areas. With several months of antibiotic treatment, outcomes tended to be good. The reports of Goldman, Rodriguez-Blanco, Hamsch and Sergeant describe a total of 10 cases who had resolution of symptoms without antimicrobials [11,13,14,23]. Notably one case series associated with permanent make-up appeared to have more complicated clinical presentation and worse outcomes [15].

RGM can be difficult to culture and mycobacteria were isolated from only 71 of the 142 reported cases. In 48 of these 71 cases, *M. chelonae* was identified. Some cases were on antimicrobials at the time of biopsy, which may account for the negative cultures. Other species less commonly found were *M. haemophilum* (12 cases), *M. abscessus* (6 cases), *M. chelonae/abscessus* group (1 case), *M. immunogenum* (1 case), *M. fortuitum* (1 case) and unspecified mycobacteria (3 cases) (note: both *M. chelonae* and *M. abscessus* were isolated from one case). These RGM have varying pathogenicity and in vitro antimicrobial susceptibilities. It is unclear which treatments are optimal but decisions may be guided by in vitro susceptibility testing [33]. *M. abscessus* is often multiply resistant and reports of

Table Panel a

Characteristics of all previously published confirmed or probable cases of tattoo-associated skin infection with rapidly growing mycobacteria from the first published case in May 2003 to December 2012 (n=142)

First author, publication year, (location of cases)[a], [source]	Number of cases: confirmed (probable)	Organisms identified (number of cases)	Characteristics	Outcome	Postulated source of infection
Wolf, May 2003, (Tel Aviv, Israel) [5]	1 (0)	Atypical mycobacteria (1)	Tattoo had dark-blue outline with green and yellow colouring. Photograph of the lesion shows spread beyond tattoo borders.	Patient refused treatment. Nodules persisted.	Not postulated.
Sungkanuparph, Sep 2003, Bangkok, Thailand [6]	1 (0)	*Mycobacterium chelonae/ abscessus* group (1)	One nodule on a tattoo.	Treated with excision and sulfamethoxazole/ trimethoprim. No relapse 15 months post-treatment.	Not postulated.
Preda, Mar 2009, Sydney, Australia [7]	1 (0)	*M. chelonae* (1)	Single artist using the same ink over 2 months of serial extensive tattooing to thigh and arm.	Substantial improvement after 4 months of clarithromycin and moxifloxacin treatment. Nodularity remained but repeat biopsy grew no mycobacteria.	*M. chelonae* sourced to a tattoo ink bottle mixed using an industrial bolt that was left in situ.
Drage, Mar 2010, Rochester, MN, United States [8]	3 (3)	*M. chelonae* (3)	Single artist in a single establishment. Lesions evolved within 1–2 weeks in grey areas of tattoos (black ink diluted with water). Black areas not affected. Median time to diagnosis of 17.6 weeks (range: 10–22.5 weeks).	One patient lost to follow-up. Five patients improved with clarithromycin (one preceded by minocycline) or azithromycin. All who completed therapy had no recurrence.	Use of non-sterile water to form grey wash. The grey wash used for these patients had been discarded. Other inks tested negative.
Lollis, Jul 2010, San Antonio, TX, United States [9]	1 (10)	*M. abscessus* and *M. chelonae* (1)	Single artist in a single establishment. Erythematous, papular eruptions in grey areas of tattoos developed 4–14 days after tattooing. One patient also developed polyarteritis syndrome.	Three patients were lost to follow-up. At 5–6 months, two cases (one on hydrocortisone cream and doxycycline, one on unspecified oral antibiotics) completely resolved but two (who received a variety of different oral and or topical treatments) had a persistent rash. No further follow-up reported.	*M. abscessus* and *M. chelonae* isolated from the grey ink used in all 11 cases. Tattoo artist reported there had been some leakage into the shipping container that held these bottles.
Bechara, Aug 2010, Paris, France [10]	1 (0)	*M. abscessus* (1)	Onset of lesions 10 days post tattoo.	Complete healing after initial treatment with pristinamycin followed by minocycline then clarithromycin. No relapse at 4-month follow-up.	Grey ink, obtained by dilution of a coloured powder with tap water, probably responsible.
Goldman, Oct 2010, Le Havre, France [11]	13 (35)	*M. chelonae* (13)	Two artists. All lesions in grey areas of tattoo.	41 patients successfully treated with clarithromycin (10 also had tobramycin). The other seven were not initially given antibiotics: lesions healed spontaneously in six patients.	Diluted black ink (diluted with saline, serum or tap water). Also syringes rinsed with tap water.
Ricciardo, Nov 2010 (Perth, Australia) [12]	1 (1)	*M. abscessus* (1)	Lesions confined to grey pigment areas.	After a variety of pre-diagnosis treatments, lesions improved with minocycline and clarithromycin. Patient ceased treatment early as flatmate with similar symptoms remained well with no treatment.	Tap or non-sterile water used to dilute black ink.

CDC: United States Centers for Disease Control and Prevention.

[a] Where location of cases is not provided in the article, first author location is given here in parentheses.

[b] The five clusters described by the CDC included the investigation of inks manufactured by four companies (A–D).

[c] The report [25] contains the preliminary details of five clusters in the United States; the Rochester, NY, cluster described in full by Kennedy et al. [24] and the four clusters listed by State. Seattle and King County, WA, had two discrete clusters, denoted as Clusters A and B.

Table Panel b

Characteristics of all previously published confirmed or probable cases of tattoo-associated skin infection with rapidly growing mycobacteria from the first published case in May 2003 to December 2012 (n=142)

First author, publication year, (location of cases)[a], [source]	Number of cases: confirmed (probable)	Organisms identified (number of cases)	Characteristics	Outcome	Postulated source of infection
Rodriguez-Blanco, Jan 2011, (La Coruña, Spain) [13]	2 (5)	*M. chelonae* (2)	Lesions restricted to grey areas. Onset 3–30 days after tattooing.	Two patients lost to follow-up. Four had a good clinical response with clarithromycin. One refused treatment but reported lesions had resolved completely on telephone follow-up.	Tap water may have been used to wash the containers used to mix inks.
Hamsch, Jan 2011, (Heidelberg, Germany) [14]	2 (5)	Undefined mycobacteria with features of *M. haemophilum* (2)	Single artist using a dark-brown ink. Granulomatous purulent skin reactions in areas around eyebrow permanent make-up application. Lesion onset days to weeks.	Three patients improved with ethambutol, clarithromycin and rifampicin. Lesions healed completely in one patient without treatment.	The dark-brown ink was found to be contaminated with a multitude of bacteria including *M. lentiflavum* and *Ralstonia pickettii*.
Giulieri, Feb 2011, (Lausanne, Switzerland) [15]	10 (2)	*M. haemophilum* (10)	Single freelance artist. Red papules or pustules, or erythematous plaque over eyebrows with lymphadenopathy after permanent make-up application. Eight patients with abscesses, in seven of these patients, the abscesses became fistulae.	Treatment with clarithromycin, ciprofloxacin and either rifabutin or rifampicin was commenced but often poorly tolerated. Only two patients responded to antibiotics and surgery was required in nine cases.	Six of 18 inks tested were positive for *M. haemophilum*. Authors postulated tap-water contamination of ink.
Wollina, Feb 2011, (Dresden, Germany) [16]	1 (0)	*M. haemophilum* (1)	Multiple tense subcutaneous nodules and cysts along right eyebrow 8 weeks after eyebrow permanent makeup application in South Asia.	Rapid and almost complete response to antibiotic therapy with clarithromycin, ciprofloxacin and rifampicin.	Not postulated.
Kappel, Apr 2011, (Los Angeles, CA, United States) [17]	1 (0)	*M. chelonae* (1)	Tender erythematous plaques and pustules confined to the grey areas within tattoos. Appeared 2 months after tattooing.	After a poor response to doxycycline, use of clarithromycin and levofloxacin lead to substantial improvement.	Not postulated.
Mitchell, Apr 2011, (Chapel Hill, NC, United States) [18] (1)	1 (0)	*M. immunogenum* (1)	Erythematous painful papules and nodules mostly within tattoo borders.	Doxycycline (stopped after 10 days) and clarithromycin given for 9 to 12 months. Continued to improve.	Possibility of some form of fluid reservoir (no further details given).
Kay, Sep 2011, (Seattle, WA, United States) [19]	1 (1)	*M. haemophilum* (1)	The confirmed case had erythematous nodules in the region of the tattoo. The probable case had a pustulo-nodular skin infection confined to shaded areas of tattoo.	The confirmed case had no response to numerous pre-diagnosis antibiotics. A course of rifampicin, ciprofloxacin and clarithromycin led to improvement and 3 months after discontinuing antibiotics, the lesions had healed.	Tap water used in a rinse solution applied during and after tattooing and to dilute ink for shading.
Binić, Dec 2011, (Kragujevac, Serbia) [20]	2 (0)	*M. chelonae* (2)	Pruritic, red lichenoid papules and plaques with scales mostly in grey areas. Three other clients from the same establishment had similar reactions but refused assessment.	Neither patient responded to various pre-diagnosis oral and topical agents. The *M. chelonae* isolated in both cases was susceptible to clarithromycin although neither treatment nor outcome are stated.	Tap water used to make grey wash from black pigment.

CDC: United States Centers for Disease Control and Prevention.

[a] Where location of cases is not provided in the article, first author location is given here in parentheses.

[b] The five clusters described by the CDC included the investigation of inks manufactured by four companies (A–D).

[c] The report [25] contains the preliminary details of five clusters in the United States; the Rochester, NY, cluster described in full by Kennedy et al. [24] and the four clusters listed by State. Seattle and King County, WA, had two discrete clusters, denoted as Clusters A and B.

Table Panel c

Characteristics of all previously published confirmed or probable cases of tattoo-associated skin infection with rapidly growing mycobacteria from the first published case in May 2003 to December 2012 (n=142)

First author, publication year, (location of cases)[a], [source]	Number of cases: confirmed (probable)	Organisms identified (number of cases)	Characteristics	Outcome	Postulated source of infection
Winthrop, Jun 2012, Portland, OR, United States [21]	1 (0)	*M. chelonae* (1)	Itchy, violaceous papules in black and grey areas of tattoo about 2 weeks after tattooing.	All lesions completely resolved after 3 months of azithromycin, linezolid and vitamin B6.	Not postulated.
Suvanasuthi, Jun 2012, (Bangkok, Thailand) [22]	1 (0)	*M. fortuitum* (1)	Three days after the tattoo session, multiple pruritic discrete erythematous papules appeared, confined to the tattoo area.	No response to one month of topical steroid and oral antihistamine. Ciprofloxacin and clarithrithromycin for a few months led to substantial clinical improvement.	This case was associated with an amateur tattoo. No specific mechanism postulated.
Sergeant, Jul 2012, Edinburgh, United Kingdom [23]	1 (3)	*M. chelonae* (1)	Single artist. Dusky, erythematous papules some with scales in grey tattooed areas.	Following failure of pre-diagnosis treatment with topical and oral agents, the eruptions in all cases later improved spontaneously. Two cases were also given clarithromycin for 6 months.	Growth of microorganisms in an opened bottle of ink demonstrated the potential for environmental contamination, although this was not the same ink used for the cases.
Kennedy, Aug 2012, Rochester, NY, United States [24] See also [25][c]	14 (5)	*M. chelonae* (14)	Single artist. All cases tattooed with ink from Company A[b]. Persistent, raised erythematous rash in grey areas within 3 weeks of tattoo.	Of the 19 patients, 18 were treated with macrolides with later addition of, or switch to, doxycycline. All 18 treated patients improved. Antimicrobial susceptibility studies were conducted in two cases; microorganisms in both these cases were sensitive to clarithromycin and doxycycline.	*M. chelonae* with indistinguishable pulsed-field gel electrophoresis pattern found in unopened bottle of ink (a grey wash hand blended by the manufacturer).
CDC, Aug 2012, Seattle and King County, WA, United States: Cluster A [25][c]	3 (0)	*M. abscessus* (3)	All cases tattooed with black ink from Company B[b]. Note: there were also 24 possible cases who did not meet our case definition.	Not stated.	Company B[b] had received complaints of long-lasting skin reactions from 35 customers in 19 states between Aug 2011 and Mar 2012. Rapidly growing mycobacteria not grown from ink or environmental samples.
CDC, Aug 2012, Seattle and King County, WA, United States: Cluster B [25][c]	2 (0)	*M. chelonae* (2)	Cases were tattooed with grey ink from Company C[b]. Note: there were also two possible cases who did not meet our case definition.	Not stated.	Sample from opened bottle of Company C ink[b] grew *M. chelonae* but pulsed-field gel electrophoresis patterns suggested it was unrelated to the isolate that was available from one of the cases in this cluster.

CDC: United States Centers for Disease Control and Prevention.

[a] Where location of cases is not provided in the article, first author location is given here in parentheses.

[b] The five clusters described by the CDC included the investigation of inks manufactured by four companies (A–D).

[c] The report [25] contains the preliminary details of five clusters in the United States; the Rochester, NY, cluster described in full by Kennedy et al. [24] and the four clusters listed by State. Seattle and King County, WA, had two discrete clusters, denoted as Clusters A and B.

Table Panel d

Characteristics of all previously published confirmed or probable cases of tattoo-associated skin infection with rapidly growing mycobacteria from the first published case in May 2003 to December 2012 (n=142)

First author, publication year, (location of cases)[a], [source]	Number of cases: confirmed (probable)	Organisms identified (number of cases)	Characteristics	Outcome	Postulated source of infection
CDC, Aug 2012, Iowa, United States [25][c]	2 (0)	*M. chelonae* (2)	Cases were tattooed with black ink from Company C[b]. Clinical isolates from both cases were indistinguishable by pulsed-field gel electrophoresis from the available clinical isolate from the Seattle and King County, WA Cluster B above.	Not stated.	Not postulated.
CDC, Aug 2012, Colorado, United States [25][c]	1 (0)	*M. chelonae* (1)	Tattooed with black ink from Company D[b].	Not stated.	Distilled or reverse-osmosis water used to dilute ink and rinse needles (when switching ink for the same client). Ink labelled as drawing ink and specified that it was not suitable for tattooing.
Curcó, Nov 2012 (Barcelona, Spain) [26]	1 (1)	*M. chelonae* (1)	Single artist. One patient had papulopustules, another had a 1 cm diameter erythematous plaque with pustules. Both had lesions confined to grey area of tattoos 2 weeks and 5 days after application respectively.	Both had initial unsuccessful treatment with topical corticosteroids and antibiotics. Lesions resolved after 3 months and less than 1 month of clarithromycin respectively.	Tattoo artist created a grey ink by mixing black ink with rose water from a local pharmacy.
Shinohara, Dec 2012 (Seattle, WA, United States) [27]	1 (0)	*M. chelonae* (1)	Burning, itching and erythematous papules and pustules noticed in grey areas of tattoo 3 weeks after application by professional mobile tattoo service.	Initial treatment with oral clarithromycin and levofloxacin. Susceptibility testing showed resistance to levofloxacin so changed to clarithromycin monotherapy. Lesions resolved completely after 4 months of treatment.	Not postulated.
Schwartzman, Dec 2012 (Los Angeles, CA, United States) [28]	1 (0)	*M. chelonae* (1)	Dramatic, diffuse blanching erythema, tenderness and warmth in both legs with a well-described nodular rash. Signs and symptoms progressed over 4 weeks.	No improvement with cefalexin treatment. After diagnosis, the patient was treated successfully with 9 months of oral clarithromycin and levofloxacin.	Not postulated.
Scott-Lang, Dec 2012 (Edinburgh, United Kingdom) [29]	1 (0)	*M. chelonae* (1)	Rash in the grey area of a tattoo. Similar rashes in other clients who attended the same studio.	Not described.	Tap water used to dilute black ink and rinse needles.

CDC: United States Centers for Disease Control and Prevention.

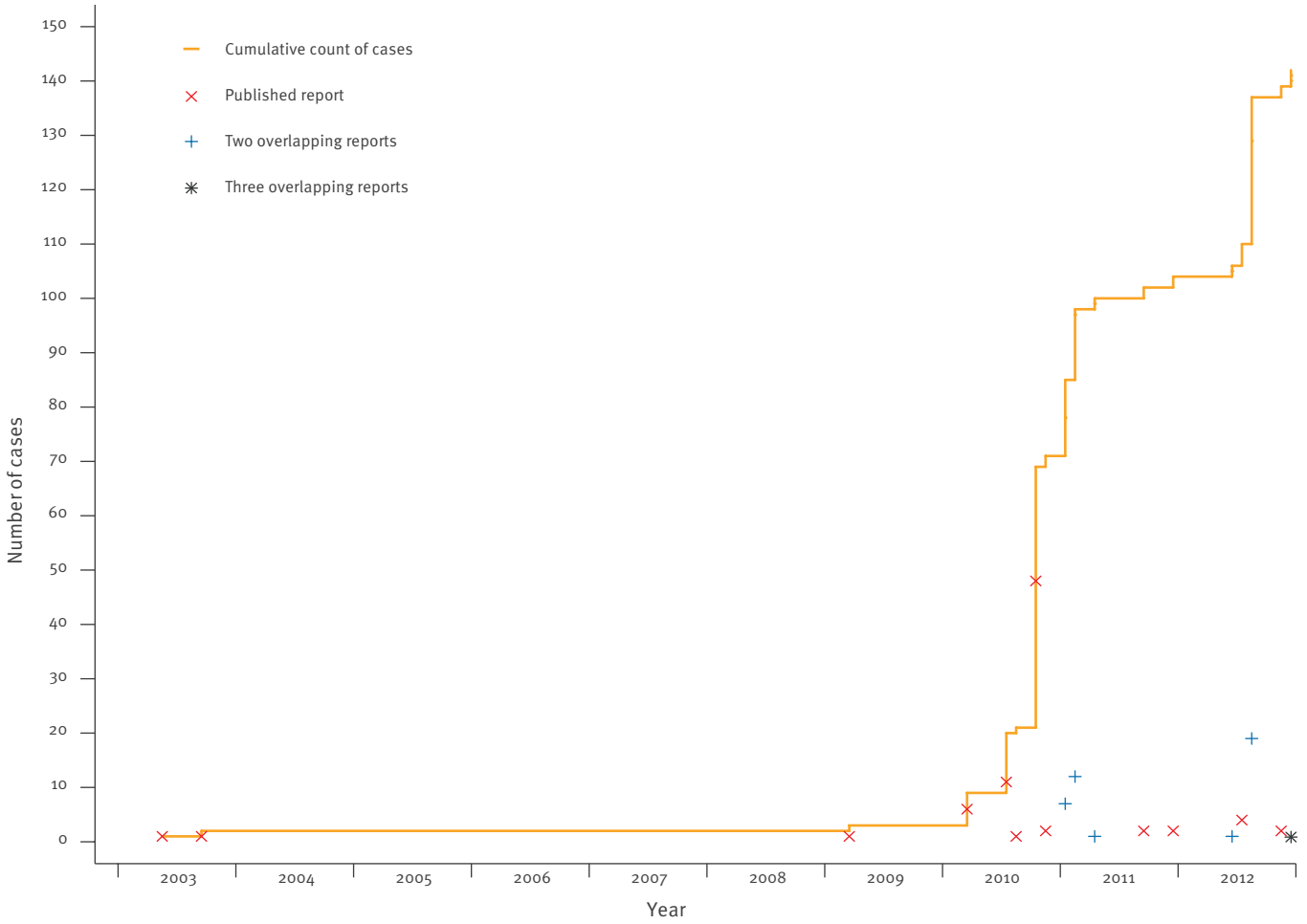
[a] Where location of cases is not provided in the article, first author location is given here in parentheses.

[b] The five clusters described by the CDC included the investigation of inks manufactured by four companies (A–D).

[c] The report [25] contains the preliminary details of five clusters in the United States; the Rochester, NY, cluster described in full by Kennedy et al. [24] and the four clusters listed by State. Seattle and King County, WA, had two discrete clusters, denoted as Clusters A and B.

Figure 3

Published confirmed or probable cases of tattoo-associated rapidly growing mycobacteria skin infection by year of publication (n=142)



Presented by published report and as a cumulative count of cases. Reports published in the same month are depicted as overlapping reports.

in vitro and in vivo antagonism should alert us to possible complications of treatment [34].

In the literature to date, contamination occurring in the tattoo studio itself has been the main postulated or identified source of RGM skin infection. The most commonly proposed mechanism is the use of non-sterile tap water to either dilute black ink to a grey 'wash' or to clean tattooing equipment, as described in 11 of the reports identified in our review. The next most frequently proposed mechanism is some other form of environmental contamination of the tattoo ink (e.g. due to breached packaging or improper handling or storage of ink). A number of investigations identified RGM or other bacteria in opened bottles of tattoo ink. In such cases, it is impossible to verify where this contamination has occurred. Kennedy et al.'s 2012 paper has been the only report to date that has identified RGM in unopened bottles of tattoo ink, suggesting contamination during manufacture or distribution [24]. The indistinguishable pulsed-field gel electrophoresis patterns in the clinical isolates from clusters in Iowa and Seattle and King County, WA, Cluster B, where cases had been tattooed with ink from the same manufacturer, would also suggest contamination occurred during manufacture or distribution [25]. Only one report described infection resulting from an amateur tattoo.

Discussion

We have summarised the characteristics of 25 published reports describing 142 confirmed and probable cases of RGM infection associated with tattooing. Estimates based on published cases are likely to underestimate the true incidence of this complication of tattooing. The frequency of published reports of this condition appears to have increased in recent years. This finding could be artefactual, driven by improved case identification (e.g. through raised clinical awareness or improvements in mycobacterial testing). Alternatively, the increase could indicate an emerging problem, potentially driven by changes in practices within the tattoo industry or the increasing popularity of tattoos. If the latter were true, one might also expect to observe increases in other tattoo-associated

infections. Unfortunately, the limited literature available on this subject is divided. For example Urbanus et al. observed that while literature from the 1980s and 1990s found an association between hepatitis B virus infection and tattooing, more recent literature rarely supports this finding [4]. Indeed a recent Dutch study by the same authors found no evidence of increased hepatitis B or C prevalence in people with multiple tattoos and/or piercings [32]. It should be noted that the Netherlands has implemented robust hygiene regulations around these procedures for a number of years, so this finding may reflect the success of national preventive measures for blood-borne virus transmission [32].

The most commonly postulated source of tattoo-associated RGM infection in the literature is contamination of tattoo ink or equipment with non-sterile water in the tattoo studio. However, the tattooist in the investigation of the Scottish cluster described and demonstrated tattooing procedures that included no such unsafe practice. In common with many similar investigations described in the literature, we were unable to obtain the actual bottles of ink used for the cases. The isolation of both *C. pauculus* and *M. chelonae* from an opened bottle of grey ink from the same studio some months later suggested contamination could have occurred in the tattoo studio. However, the ubiquitous nature of these microorganisms in the environment means that contamination during collection or processing of environmental samples remains a possibility.

Contamination during production or distribution of the ink is also a possibility. Our cluster investigation did not identify any further cases in the UK at the time, nor did we find any evidence of contamination in unopened ink samples sourced from the distributor. This was the best, albeit weak, evidence that we could pragmatically gather against contamination having occurred higher in the supply chain in our investigation.

Recent analyses of a wide range of commercially available tattoo inks demonstrated surprisingly high rates of bacterial contamination in both open and unopened ink bottles [35,36]. The most recent of these noted that 10% of unopened ink bottles tested were contaminated, 28% had inadequate physical sealing and a number made false claims of sterility [36]. These studies did not test specifically for RGM.

A search for 'tattoo ink' on the European Union Rapid Alert System for non-food dangerous products (RAPEX) website [37] identified five occurrences of tattoo inks being banned, recalled or withdrawn because of bacterial contamination since 2005. None of these instances involved RGM, although it is possible that culture techniques appropriate for mycobacteria were not employed during testing. These occurrences are consistent with the high prevalence of bacterial contamination in tattoo inks, identified in the studies above. It was perhaps unsurprising that, in 2012, Kennedy et al. described the first reported outbreak in which RGM (indistinguishable from those in clinical samples by pulsed-field gel electrophoresis) were identified in unopened bottles of the same brand of premixed ink that was used for the tattoos [24].

Manufacturing requirements in Europe and the United States tend to treat tattoo inks as cosmetic substances, with much less stringent controls than for medical products that are injected [36,38,39]. Within Europe, recommendations have been produced that include a requirement of sterility for tattoo ink – for example, the European Council tattoo regulations [40]. However, few countries have adopted such regulations to date, although the existence of empirical data demonstrating high rates of tattoo ink contamination may help change this [35,36].

The sterilisation of tattoo inks is not straightforward. Filter sterilisation would also remove the coloured particulates that give the ink its character. One alternative is to use industrial gamma-irradiation and we are aware of a number of tattoo suppliers in the UK that employ this approach. We have heard of anecdotal concerns regarding the potential for decomposition of ink constituents following irradiation but were unable to find any published evidence of this phenomenon, nor of the safety or effectiveness of this technique.

Our public health investigation could not confirm the point of contamination in the Scottish cluster. Analyses of inks on the market, combined with recent clusters in the United States, suggest that quality control measures for tattoo inks clearly need to be improved to ensure a sterile product is produced. However, the identification of unsafe practice in tattoo studios in many reports suggests that efforts also need to continue to be focused here. Any such interventions must balance the benefits of stricter controls with the risks of alienating the tattoo industry or increasing tattoo prices as these, in turn, could increase the prevalence of illegal tattooing with potentially grave public health consequences.

Acknowledgements

The authors would like to thank Carole-Ann Wright and Colin Sibbald from the City of Edinburgh Council, Louise Joyner from Christchurch Borough Council, Dorset, and the staff at both the Edinburgh Scientific Services and the Scottish Mycobacteria Reference Laboratory (SMRL) for their invaluable assistance with these investigations (SMRL laboratory work is carried out as part of the remit of the SMRL, funded through its contract with Health Protection Scotland and National Services Scotland). We would also like to thank Dr Alan Beswick from the Health and Safety Laboratory for his expert advice; and Martin Higgins from NHS Lothian, Dr David McAllister from the University of Edinburgh and Dr Catherine O'Connor from the Health Protection Agency for their incisive comments on the manuscript. Finally, we would like to thank the reviewers for their thorough and helpful scrutiny.

This review was not supported by external funding.

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International infectious disease surveillance during the London Olympic and Paralympic Games 2012: process and outcomes

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Citation style for this article:
Jones J, Lawrence J, Payne Hallström L, Mantero J, Kirkbride H, Walsh A, Jermacane D, Simons H, Hansford KM, Bennett E, Catchpole M, on behalf of the international team. International infectious disease surveillance during the London Olympic and Paralympic Games 2012: process and outcomes. Euro Surveill. 2013;18(32):pii=20554. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20554

Article submitted on 14 November 2012 / published on 08 August 2013

Surveillance for possible international infectious disease threats to the Olympic and Paralympic Games in London, United Kingdom, was conducted from 2 July to 12 September 2012 by a collaborative team comprising representatives from the Health Protection Agency (Public Health England since April 2013), the European Centre for Disease Prevention and Control and the National Travel Health Network and Centre. Team members enhanced their usual international surveillance activities and undertook joint risk assessments of incidents identified as relevant through an agreed set of criteria designed for the Games and using tools developed for this purpose. Although team members responded to a range of international disease incidents as part of their routine roles during this period, no incident was identified that represented a threat to the Games. Six incidents were highlighted by the team that were likely to attract media attention and hence could generate political and public concern. Responding to such concern is an important aspect of the overall public health management of mass gathering events. The lessons learned about the process and outcomes of the enhanced international surveillance will help inform planning by future hosts of similar events.

Introduction

The Olympic Games are the largest international sporting 'mass gathering' event in the world, followed by the Paralympic Games. In 2012, both events were hosted by the United Kingdom (UK), centred on the Olympic Park in East London, but with events also taking place in other venues across the country. The Games took place from 27 July to 12 August (Olympics) and from 29 August to 9 September (Paralympics). More than 25,000 athletes and officials took part from over 200 countries. Many more tens of thousands of journalists, workers and volunteers were also involved, with total spectator attendance estimated to be around 10 million across both events at all venues combined.

In common with other mass gatherings, large international sports events present a range of complex challenges to host countries, including public health preparedness [1]. The types of infectious disease (ID) incidents that are relevant for mass gatherings have been previously described [2], but none were reported in association with any of the last four Olympic Games [3]. Considerable concern is, however, generated by the potential impact of such incidents on the Games, the host population and countries to which athletes and visitors return. Highly infectious diseases with airborne/droplet transmission and short incubation periods pose the greatest potential threat to large public gatherings such as the Games and there are examples where such infections have been transmitted in similar contexts [4-7]. Considerable effort is directed towards early identification of potential ID threats associated with such events, often including those that may arise outside the host country [8,9], so that appropriate responses may mitigate any significant risk detected.

With high levels of global travel, migration and economic interdependence as well as increased speed of transport around the world, international ID surveillance is now an important and routine part of many

countries' general public health preparedness. Both the World Health Organization (WHO) and the European Commission have established restricted-access web-based communication platforms so that Member States can share information about public health incidents; these include the WHO Event Information Site for International Health Regulations (IHR) national focal points and the European Early Warning and Response System (EWRS). These platforms provide alerts about significant international public health incidents to Member States, which may also perform additional information gathering of their own.

Epidemic Intelligence (EI) is a form of surveillance that refers to a process of rapid systematic collection, collation, validation, analysis and risk assessment of information about potential public health incidents from a variety of sources [10,11]. Its purpose is to permit earlier detection of potential health threats so that timely public health responses can be recommended and enacted. EI activities are implemented at different levels and using various modalities by many national and international public health institutions. They complement standard surveillance data with formal and informal reports about incidents of potential public health relevance (event-based surveillance, EBS) [12]. EBS has been revolutionised in the last 10 years by the rapid development of web technologies and electronic communication: these changes have defined a crucial role for open access online information for risk detection and monitoring activities, although they have also greatly increased the amount of background 'noise' of ID incidents requiring evaluation.

International ID surveillance for the 2012 Olympics and Paralympics (also known as London 2012) was conducted by a collaborative 'international team' comprising several organisations that have routine roles in EI. The work of these groups overlaps to a certain degree, but each has its own particular responsibilities and therefore also its own criteria for selection of items for further monitoring, assessment or response, as outlined below.

- The National Travel Health Network and Centre (NaTHNaC) and the Travel and Migrant Health Section (TMHS) of the Health Protection Agency (HPA) (Public Health England since 1 April 2013, but referred to throughout this article as the former organisation) are primarily concerned with international ID incidents that may have an impact on British travellers. They also produce clinical updates for health professionals about relevant incidents [13].
- The Emerging Infections and Zoonoses (EIZ) and Microbial Risk Assessment (MRA) sections of the HPA are concerned with assessing and responding to potential ID threats to UK public health. They provide evidence-based risk assessments of ID incidents to inform policy, planning, public health countermeasures and communications. Both sections produce regular summaries of potential threats for relevant professionals.
- The European Centre for Disease Prevention and Control (ECDC) is concerned with detecting, monitoring, assessing and communicating ID issues of concern to the European Union and supporting the coordinated response to potential ID threats to the public health of the European Union [14]. ECDC produces regular reports, epidemiological updates and risk assessments.

The primary purpose of international ID surveillance during London 2012 was to identify ID incidents occurring anywhere in the world outside the UK that might have an adverse impact on London 2012, e.g. by affecting the health of competitors/visitors/others involved in the Games (with or without potential for subsequent export of disease from the UK and/or spread within the UK), or by affecting the smooth running of the Games and/or travel to and from the UK or by attracting media attention/public and political concern irrespective of whether that concern was justifiable.

Secondary purposes included identifying international ID incidents during London 2012 that might require provision of advice to clinicians seeing imported cases, or implementation of particular public/port health measures.

This paper outlines the international ID surveillance carried out during London 2012 and describes the results generated during the 10.5-week (73 days) enhanced surveillance period, along with its personnel requirements. It also aims to share lessons learned about the process and outcomes of this, as compared with routine activity, to help inform planning by future hosts of similar events.

Methods

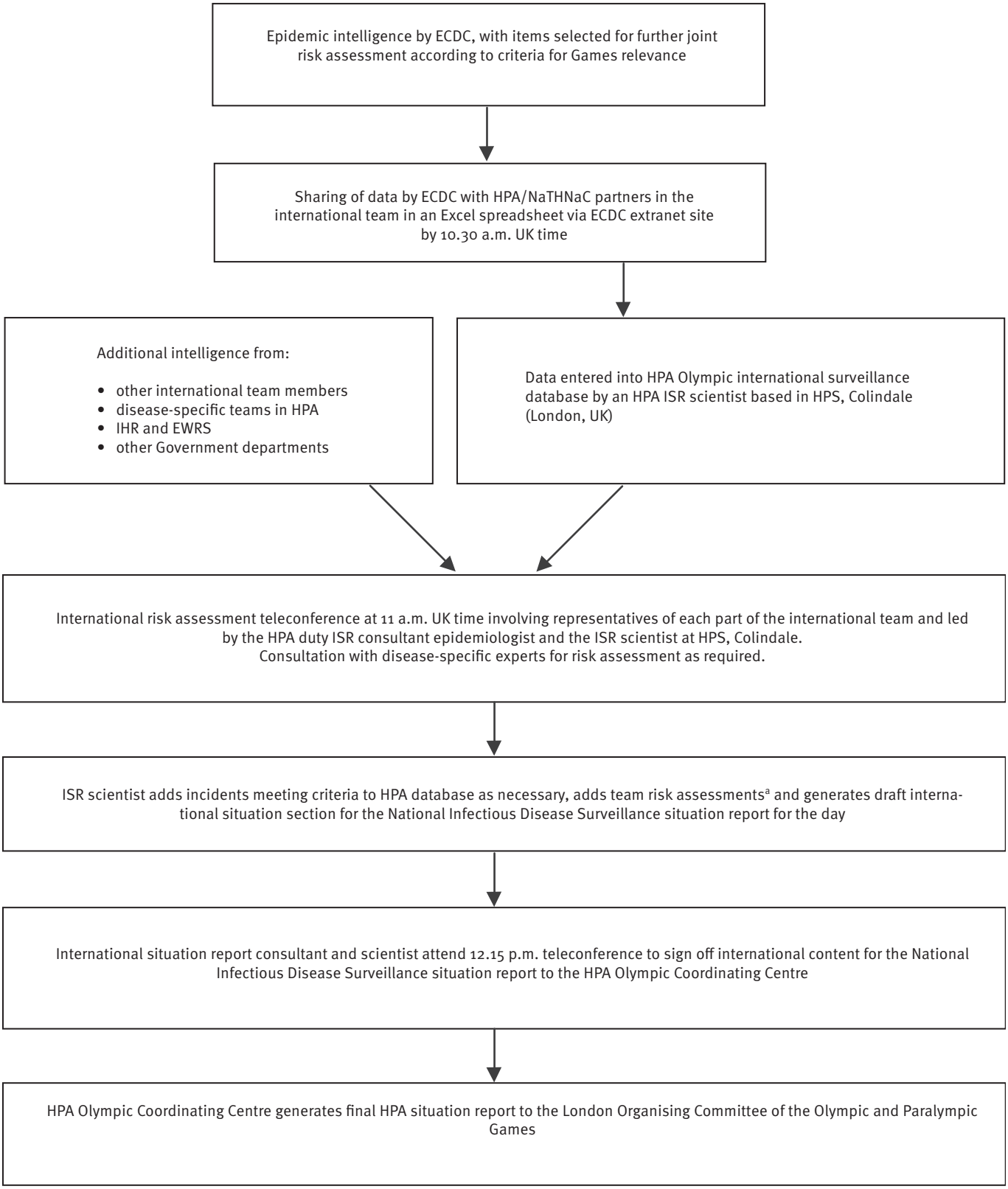
International surveillance for London 2012 was based on an enhanced 'business as usual' model and was part of wider surveillance activity that has been previously described [3]. The international team began working together early in 2010 and over the next two years, developed an enhancement of their normal processes that was extensively tested and refined to maximise sensitivity and specificity of identification of ID incidents relevant for the Games, and to use resources efficiently.

The process adopted for daily international surveillance is outlined in Figure 1. Of the collaborating groups, only ECDC has a dedicated unit that undertakes extensive EI on a 24/7 basis. Thus they led on this aspect of the process, enhancing and modifying their work to provide tailored support for the HPA to detect, monitor and assess potential international ID risks to London 2012.

ECDC EI activity focuses primarily on the use of open access web-based information. ECDC has collaborated

Figure 1

Daily scheme for international surveillance during the London Olympic and Paralympic Games 2012 (2 July–12 September 2012)



ECDC: European Centre for Disease Prevention and Control; EWRS: European Early Warning and Response System; HPA: Health Protection Agency (now Public Health England); HPS: Health Protection Services; IHR: International Health Regulations; ISR: international situation report; NaTHNaC: National Travel Health Network and Centre; UK: United Kingdom.

[a] In assessing the risk of selected items for inclusion in the daily situation report the following factors were considered: background epidemiology, number/demographics of people affected, setting, clinical severity, person-to-person transmissibility, likely connections between the affected population and Games attendees and or the UK population, ease of control, source of infection if known, how well the disease is understood, potential for spread and reliability of the source of the intelligence.

Table 1

Resources to support the international infectious disease incident surveillance function during London Olympic and Paralympic Games 2012 (2 July–12 September 2012)

Resource category	Resource and lead developer	New/ pre-existing/ modified	Description
Epidemic intelligence	Event-based surveillance systems (ECDC)	Modified	Open-access web-based information (media and official sources): • Global Public Health Intelligence Network, (GPHIN) (Public Health Agency of Canada) [27] • HealthMap (Harvard-MIT Division of Health Sciences and Technology, Boston, United States) [28] • MedISys (Joint Research Centre, European Commission) [29] • PULS, Pattern-based Understanding and Learning System (University of Helsinki, Finland) [30].
	Epidemic Intelligence Information System, EPIS (ECDC) [31]	Pre-existing	A communication platform tool that allows exchange of non-structured and semi-structured information regarding current or emerging public health threats with a potential impact in the European Union.
	Routine fortnightly surveillance of influenza in the southern hemisphere (ECDC)	Pre-existing	A combination of epidemic intelligence and more conventional surveillance that is used after pandemics and other changes in influenza viruses and which was reactivated for London 2012.
	Weekly surveillance of measles outbreaks worldwide (ECDC)	Modified	A combination of epidemic intelligence and more conventional surveillance sources.
	Criteria for London 2012 relevance (HPA, TMHS)	New	See Table 2.
Databases	Threat tracking tool [31] (ECDC)	Modified	An internal ECDC-designed sharepoint platform that acts as a document repository and reporting tool (e.g. producing the daily and weekly ECDC reports). Dedicated sections of the tool were created for storing detailed information on relevant screened items and internal actions by ECDC.
	HPA Olympic international surveillance database (HPA, TMHS)	New	An Access database in which all incidents identified that met London 2012 relevance criteria were recorded in a standardised way, risk assessments added and situation reports generated automatically.
Communication	Extranet (ECDC)	New	Password protected communication portal for sharing a database of daily screening results, information, protocols etc that all members of international team could access.
	Shared drive (HPS, Colindale)	New	Shared network drive for all members of the team based in HPS-Colindale to share information.
Protocols	Standard operating procedures (HPA, TMHS, ECDC)	New	Comprehensive guidance for all team members on daily processes.
	International risk assessment teleconference resources (HPA, TMHS)	New	Standard agenda for daily teleconferences with constant dial-in details and template for recording minutes.
Risk assessment support tools	Epidemiological profiles (HPA, TMHS and EIZ)	New	Up-to-date global epidemiology of a wide range of diseases including recent outbreaks.
	Travel patterns (HPA, TMHS)	New	Tables of historical travel connections for the months July to September inclusive between the United Kingdom and the rest of the world based on International Passenger Survey data [20].
	Risk definitions (HPA, EIZ)	Pre-existing	Standard definitions of risk levels.

ECDC: European Centre for Disease Prevention and Control; EIZ: Emerging Infections and Zoonoses; HPA: Health Protection Agency (now Public Health England); HPS: Health Protection Services; MIT: Massachusetts Institute of Technology; TMHS: Travel and Migrant Health Section.

Box

Criteria used during epidemic intelligence activity to select international infectious disease incidents of possible relevance to the London Olympic and Paralympic Games 2012 (2 July–12 September 2012)

Incidents generally excluded from further risk assessment unless significant change in epidemiology/clinical picture/potential for international spread

- Chronic infectious disease of long latency, e.g. TB, HIV, chronic hepatitis B or C.
- Arthropod-borne disease with no current evidence for the occurrence of autochthonous transmission in the UK, e.g. malaria, dengue, chikungunya, leishmaniasis, yellow fever.
- Diseases that are normally endemic in the global area being reported with no significant change in epidemiology/clinical picture/ implications for international spread.
- Localised outbreaks of gastrointestinal disease, unless an internationally distributed food source is implicated, or verocytotoxin-producing *Escherichia coli* (VTEC), or highly infectious person-to-person with large numbers affected e.g. norovirus.
- Outbreaks in defined population groups, e.g. school/hospital/refugee camp, where there is little chance of spread to the wider population, unless very unusual or severe.
- Environmentally acquired infections e.g. Legionnaires' disease.
- Sporadic cases of plague/anthrax/botulism or other agents that may be associated with bioterrorism but where the case has an obvious zoonotic exposure.

Incidents generally included for further risk assessment

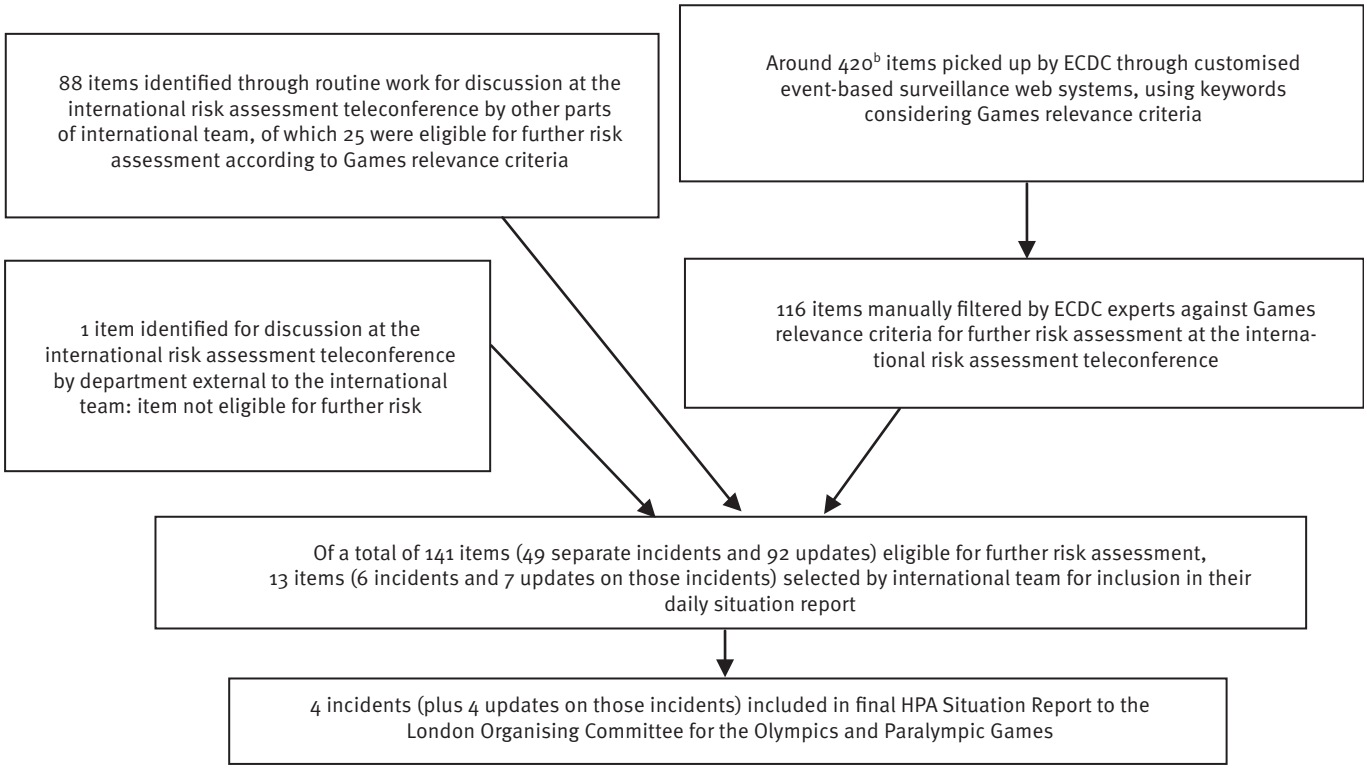
- Respiratory disease:
  - new incidents of influenza among humans, especially with a new subtype;
  - new incidents of Severe Acute Respiratory Syndrome
  - new incidents of other acute and severe respiratory infections, with or without a microbiological diagnosis.
- Gastrointestinal disease:
  - with significant changes in epidemiology/clinical picture;
  - large[a] outbreaks of viral infection spread by person to person contact, e.g. norovirus;
  - VTEC: significant numbers of cases over a short time frame in a small area;
  - if an internationally distributed food source is implicated.
- Vaccine-preventable disease where there has been a significant change in epidemiology in the global area being reported.
- Large[a] outbreaks or a change in clinical picture of meningococcal disease/encephalitides.
- Large[a] outbreaks or a change in clinical picture of sexually transmitted infection.
- Significant changes in the antibiotic resistance of an organism causing an outbreak.
- Zoonotic disease:
  - new incidents of avian influenza in birds in a previously unaffected area, especially with a new virus subtype;
  - other zoonotic disease that may have direct implications for the Games e.g. in horses.
- Incidents of serious undiagnosed illness of any type, especially with a high morbidity/mortality.
- Incidents of acute syndromes without a definitive diagnosis (e.g. fever, rash, jaundice, neurological, diarrhoea and vomiting, respiratory).
- Any incident of a disease with an unexpectedly high morbidity or mortality.
- Clusters of imported disease reported from countries outside the UK, which imply a problem in a third country and from which disease has not been previously reported.
- Incidents on cruise ships where the ship is destined for the UK.
- Any incident of disease with a significant potential for international spread.
- Any incident of disease that may interfere with trade or travel as advised by WHO or Foreign and Commonwealth Office.
- Any incident occurring outside the UK that might attract significant UK media attention or public or political interest.

HIV: human immunodeficiency virus: TB: tuberculosis; UK: United Kingdom; WHO: World Health Organization.

[a] Where 'large' is defined relative to the history of any previous outbreaks.

Figure 2

Results of enhanced daily international infectious disease surveillance for the London Olympic and Paralympic Games 2012 (2 July–12 September 2012)[a]



ECDC: European Centre for Disease Prevention and Control. HPA: Health Protection Agency (now Public Health England)

[a] Note that this does not include the weekly measles and fortnightly influenza surveillance activity.
[b] Estimation after de-duplication for language.

with the developers of several EBS web systems that are able to gather, filter and classify public health information in real-time. Most of these systems are fully automated; however, some of them include a human filtering component. The EBS systems that were modified for the specific surveillance needs of London 2012 are shown in Table 1. In addition to these systems, information was also obtained from online discussion forums, restricted-access website communication platforms for disease-specific European surveillance networks coordinated by ECDC, and other network sources for evaluation of anticipated threats, such as influenza epidemics in the southern hemisphere.

The criteria that were developed by the international team for ECDC to use to select ID incidents through their EI activity for further joint risk assessment are summarised in the Box. These criteria were aligned with the purposes of the surveillance activity as described above and were informed by a shared evidence-based understanding of the types of international ID incidents that would have the potential to have an impact on the Games. Other parts of the international team contributed information from their own routine EI activity if it fulfilled these criteria, and all contributed to the joint risk assessment of incidents for the Games by means of a daily international risk assessment teleconference. Information about any international incidents identified by any HPA or other Government department personnel (e.g. Department of Health/Foreign and Commonwealth Office) were requested to be sent to the international team led from Health Protection Services, Colindale, rather than independently reported, so that all were subject to the same risk assessment process and a standard risk language was used to report them. Only newly reported incidents or significant changes to baseline epidemiology/clinical picture (e.g. increased severity) or significant changes to the status of ongoing incidents were considered for inclusion in the daily international situation report. In addition to the daily reporting, summaries of any significant changes in global measles and influenza epidemiology were also provided by the international team on a weekly and fortnightly basis respectively.

Table 2

Outcome of routine epidemic intelligence undertaken by parts of the international team during the surveillance period but outside the specific context of the London Olympic and Paralympic Games 2012 (2 July–12 September 2012)

Part of international team	Outcome of routine work outside Olympic context during 2 July to 12 September 2012
NaTHNaC and TMHS	• 401 items indentified against NaTHNaC criteria for relevance to United Kingdom travellers (including both incidents and updates to incidents) for inclusion in NaTHNaC Outbreak Surveillance Database and in Daily Briefs to service users • 24 clinical updates posted on NaTHNaC websit
EIZ	• 305 items (including both incidents and updates to incidents) meeting EIZ criteria noted in daily log • 2 monthly Emerging Infection summaries produced giving details of 26 incidents of interest • Responded to 4 international infectious disease incidents
MRA	• 964 items (including both incidents and updates to incidents) meeting MRA criteria included in the MRA database • 10 weekly and 2 monthly reports produced including these incidents
ECDC	• 250 total items (including both incidents and updates to incidents) meeting ECDC routine criteria brought to daily ECDC risk assessment meeting • 8 new incidents included in the threat tracker tool • 6 incidents under continuous monitoring • 11 weekly Communicable Disease Threat Reports • 10 Rapid Risk Assessments • 4 Epidemiological Updates

ECDC: European Centre for Disease Prevention and Control; EIZ: Emerging Infections and Zoonoses; MRA: Microbial Risk Assessment; NaTHNaC: National Travel Health Network and Centre; TMHS: Travel and Migrant Health Section.

Note that TMHS, EIZ and MRA are all sections of the Health Protection Agency (now Public Health England).

Table 1 summarises the range of resources that were required to support the international surveillance function. Rotas were developed to cover necessary duties seven days a week throughout the London 2012 surveillance period. The HPA seconded four public health trainees to ECDC to support EI activity, and a liaison officer from ECDC was also stationed with the national and international infectious disease surveillance departments based at Colindale during the three weeks of the Olympics to facilitate the day-to-day collaboration.

Analysis of ID incidents identified during the surveillance period comprised: (i) analysis of incidents that fulfilled the criteria (all those contained within the HPA Olympic international surveillance database); and (ii) analysis of other incidents discussed at the international risk assessment teleconference but which did not fulfil the criteria and were not therefore imported into the database. This involved detailed review of all notes from the daily teleconference. All incidents were analysed in Microsoft Excel.

Results

The results of daily international surveillance for London 2012 for the entire surveillance period are summarised in Figure 2. In total, 49 separate incidents were identified as relevant according to the Games criteria and therefore required further risk assessment by the international team. Of these, 17 were related to gastrointestinal infections such as salmonellosis, cholera and *Escherichia coli* infection, 12 to childhood infections such as hand, foot and mouth disease, pertussis and measles, seven to influenza, seven to zoonoses such as anthrax and those due to infection with West Nile virus, hantavirus and Hendra virus, three to viral haemorrhagic fevers such as Lassa and Ebola and a further three to other infections. In terms of the geographical location of these incidents, 18 were reported in Europe, 10 in North America, eight in Asia, seven in Africa, four in Oceania and two in South and Central America. Of the 17 gastrointestinal disease incidents, nine had specific foods implicated as the source and the international team followed up six of these with the UK Food Standards Agency. None of these incidents involved food that was known to be imported into the UK.

The international team highlighted 13 items (six incidents and seven updates on those incidents) in their daily contributions to the national infectious disease surveillance situation report. None of these were assessed as posing an actual threat to the Games; however, all fulfilled the criterion of potentially 'attracting significant UK media attention or public or political interest'. The six new incidents included (with the initial source of the information) were:

1. Acute respiratory syndrome in Cambodia, later confirmed as hand, foot and mouth disease caused by enterovirus-71 (IHR)
2. Acute watery diarrhoea in Cuba, later confirmed as cholera (Cuban Ministry of Health)

Table 3

Estimated additional person-hours required over and above routine work for enhanced international infectious disease surveillance during the London Olympic and Paralympic Games 2012 (2 July–12 September 2012)

Site of team	Total number of staff involved in rota	Estimated average minutes of total time per day over and above routine work (a)	Total additional hours over whole surveillance period of 73 days[a]
HPS Colindale	6 ISR scientists	120	146
	5 ISR consultants	90	110
MRA[b]	3 scientists/risk assessors	45	40
NaTHNaC[b]	1 information officer	50	44
	5 clinical practitioners	40	35
ECDC	7 duty officers	65	79
	6 epidemic intelligence mass gathering and other disease experts	120	146
	5 trainees	120	146
Total all sites	–	–	**746**

ECDC: European Centre for Disease Prevention and Control; ISR: international situation report; HPS: Health Protection Services; MRA: Microbial Risk Assessment; NaTHNaC: National Travel Health Network and Centre.

Note that HPS and MRA are parts of the Health Protection Agency (now Public Health England).

[a] Calculation: (a) x total number of days/60.

[b] Involved Monday to Friday only (53 days in total).

3. Swine-origin H3N2v influenza A in the United States (IHR)
4. Ebola in Uganda (WHO and Ugandan Government)
5. Cholera in Nepal (media report)
6. Hantavirus pulmonary syndrome in Yosemite National Park, United States (United States Centers for Disease Control and Prevention).

Incidents 1, 2, 4 and 6 (plus four updates to these incidents) were included in the final HPA daily situation report to the London Organising Committee for the Olympics and Paralympic Games by the HPA Olympics Coordinating Centre. Throughout the surveillance period, although the southern hemisphere influenza season had started and there were ongoing outbreaks of measles in several countries, there were no significant and/or unexpected changes to the global epidemiology of measles or influenza of relevance to London 2012.

Of the six incidents above, five were notified to the UK under the IHR: two were first identified through IHR and three were first identified through publicly available media and state sources and later reported under the IHR. The time gain of EI over IHR reporting in each case was 3 days (hantavirus pulmonary syndrome in the United States), 10 days (cholera in Cuba) and 15 days (Ebola in Uganda).

The outputs from the simultaneous routine EI activity undertaken by the individual parts of the international team outside the Olympic context are summarised in Table 2.

The personnel time required for operation of the enhanced international surveillance system is illustrated in Table 3. In total, 746 additional person-hours over and above routine roles were engaged in Games-specific activity throughout the surveillance period. This does not include the planning, preparation and exercising time by team members in the preceding two-year period.

Discussion

During the London 2012 surveillance period, the individual parts of the international team continued their routine EI work as well as looking specifically for international ID incidents that might have an impact on the Games. International ID incidents occur all the time and Table 2 demonstrates that over the London 2012 surveillance period, the individual parts of the international team identified and responded to a considerable number of incidents as part of their routine work because they were relevant in some way to their public health perspectives. No international incidents detected during the surveillance period were assessed as likely to pose a disease threat to the Games and no public health responses were therefore developed. It is significant that the only incidents reported by the

international team were those that were judged (on the basis of past UK experience) as being likely to attract media attention and hence possible political and public concern. Alerting the press office to the possibility of media interest so that responses can be developed as necessary is an important aspect of the overall public health management of large public events.

The combination of the enhanced EI work of ECDC, supplemented by the routine EI work of the various groups in the international team, gave the system high sensitivity for detection of potential threats. It is very unlikely that any incidents of significance for the Games were missed – a view reinforced by the fact that during the surveillance period there were no reports of ID incidents associated with the Games that were linked to overseas incidents. The incident selection criteria developed for EI also gave the process high specificity, thus improving the efficiency of the joint risk assessment process.

The fact that no international ID incidents likely to impact on London 2012 were identified is perhaps not surprising. Likelihood of impact on an event from an overseas ID incident will broadly depend on the nature of the disease (including mode of transmission and incubation period), the number of cases likely to be imported in a relevant time frame (which in turn depends on population connections between the location of the international incident and the host country and, in particular, attendees of the event), the nature of the event, and the ID epidemiology and public health preparedness of the host country. The sanitary and public health infrastructure in the UK, and the absence of the requisite arthropods and/or environmental conditions for most tropical vector-borne diseases, both reduce the likelihood that importation of cases of many types of disease might lead to significant public health issues, either in or out of the Games context. The same may not be true for other countries that might host mass gathering events. The criteria that different countries will use in determining which international ID incidents might be significant in relation to any large public events they host will therefore vary according to their particular circumstances, their normal public health concerns and the nature of the event. The risks associated with a large international sporting event such as London 2012 are likely to be different from those associated with a large international religious event such as the Hajj [15]. Large public events occur very frequently in the UK and associated outbreaks of indigenous ID have occasionally been recorded [16-18].. Literature searches, however, identify no reports of large public events in the UK affected by international ID incidents.

Although athletes /officials and spectators attended London 2012 from all over the world, the majority of the nearly 600,000 international visitors to the UK in July and August who came wholly or partly for London 2012 were from mainland Europe [19]. It must be remembered that the UK, and London in particular, is a very popular travel destination. During July to September each year, on average 9 million people visit the UK from overseas and nearly half of these include at least one overnight stay in London [20]. Although the overall epidemiology of ID in the UK is influenced by international population movement [21], with some examples of generally small-scale outbreaks associated with imported disease [22], it is rare for acute ID incidents occurring elsewhere in the world to have a significant impact on the UK, despite the global connectedness of London. This is partly for the reasons outlined above but also because ID incidents that involve significant international spread, while unpredictable, are infrequent. Since the implementation of the latest IHR (IHR 2005) in 2007, the Director-General of WHO has declared only one public health emergency of international concern (pandemic influenza A(H1N1) in 2009 [23]) and before that, the most recent serious global ID incident was Severe Acute Respiratory Syndrome (SARS) in 2003. Influenza A(H1N1)pdm09 involved global transmission over a period of months during which several mass gathering events took place with control measures implemented on a precautionary basis to minimise any potential public health impact [24-26].

The considerable time commitment in the two-year planning and preparation stage by the international team was invaluable. By the time the London 2012 surveillance period began, the enhanced process was established, the supporting resources were all developed and the activity quickly became part of the daily routine, thus allowing most of those involved to continue with their normal non-London 2012 roles. During the operational stage, international surveillance for London 2012 required a total of around 10 additional hours of personnel time per day, and resources available were used in the most efficient way possible by appropriate division of labour. In particular, ECDC had the lead expertise and responsibility for EI activity, enhancing their usual function in this regard, while the HPA took the lead in the risk assessment process. The international collaboration between UK partners and ECDC worked extremely well and also provided valuable training opportunities, with the involvement of both UK public health trainees and a European Programme for Intervention and Epidemiology Training (EPIET) fellow in ECDC activities. Some incidents included in the international situation reports were detected earlier as a result of EI, which could be very important for an actual threat in terms of response. Perhaps a more significant advantage of the robust system developed was, however, the continuous monitoring of incidents and real-time sharing of relevant information for assessment by a group of experts. Early trials demonstrated that there was value in conducting risk assessments with representatives from all parts of the team, since each group brought its own perspective and experience from routine work. Standardising the approach to assess incidents and report on risk, and having only one route for international information in the overall London 2012

surveillance system, were also demonstrated to be valuable in exercises.

The international surveillance model used worked well for the London 2012 situation and resources available. This does not, however, mean that this model is necessary for all other countries hosting similar events in the future. Of the six items identified for inclusion in the daily international situation report, five were reported to Member States by WHO under IHR, though there were time lags associated with three of these. Countries hosting large sporting events in the future will need to consider to what degree they will need to supplement alerting systems such as these with their own, and/or collaborative, EI processes, when determining how to allocate resources to international surveillance among the wide range of public health responses required for such events.

Acknowledgements

ECDC: Lara Payne Hallström, Jas Mantero, Assimoula Economopoulou, Pasi Penttinen, Angus Nicoll, Edit Szegedi, Sergio Brusin, Bertrand Sudre, Niklas Danielsson, Gianfranco Spiteri, Niels Kleinkauf, Erika Duffell, Edoardo Colzani, Gayle Dolan (UK public health trainee seconded to ECDC), Gavin Dabrera (UK public health trainee seconded to ECDC), Jillian Johnston (UK public health trainee seconded to ECDC), Philip Veal (UK public health trainee seconded to ECDC), Pete Kinross (EPIET fellow); **HPA, Health Protection Services, Colindale:** Jane Jones, Joanne Lawrence, Karen Wagner, Edgar Wellington, Katie Geary, Hilary Kirkbride, Amanda Walsh, Bengü Said, Dilys Morgan, Catherine O'Connor, Katherine Henderson, Ruth Ruggles; **HPA, Microbial Risk Assessment & Behavioural Science, Emergency Response Department, Health Protection Services, Porton Down:** Kayleigh Hansford, Emma Bennett, Maaike Pietzsch; **National Travel Health Network and Centre:** Daiga Jermacane, Hilary Simons, Claire Wong, Lisa Ford, Dipti Patel, Vanessa Field.

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